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# HODGKIN'S DISEASE*

## V. Involvement of Certain Other Organs

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THE preceding article covered the involvement of the hilar nodes, lungs, gastrointestinal tract, bones and skin by Hodgkin's disease. In this paper the involvement of certain other organs will be discussed.

### LYMPH NODES

*Hodgkin's Paragranuloma*

In Hodgkin's paragranuloma, the peripheral lymph nodes, most frequently those in the neck, are invariably involved. Indeed, the initial symptom of the condition is almost always peripheral lymphadenopathy. The medastinal lymph nodes are involved in approximately one third of the cases. Unless such mediastinal involvement is massive or there are indications that the condition is progressing into Hodgkin's granuloma, the prognosis is not necessarily poor.

*Hodgkin's Granuloma*

In Hodgkin's granuloma, lymphadenopathy in one region or another often brings the physician's or the patient's attention to the presence of the disease. By far the most frequent site for lymphadenopathy at the onset is in the neck, and as has already been pointed out, mediastinal enlargement without peripheral lymphadenopathy is extremely rare (Table 1).

TABLE 1. *Initial Lymphadenopathy in 213 Cases of Hodgkin's Granuloma.*

| LYMPHADENOPATHY | NO. OF CASES |
|---|---|
| Cervical | 154 |
| Axillary | 27 |
| Inguinal | 15 |
| Mediastinal | 4 |
| None | 13 |

The superficial lymph nodes in one or another part of the body sooner or later are almost invariably involved, and it has already been noted that by far the most frequent initial symptom is cervical lymphadenopathy, although this may not be noticed by the patient. The characteristics of the enlarged nodes have already been referred to.

There is some disagreement among investigators concerning the most frequent sites of the lymphadenopathy, the source of confusion often being failure to state whether clinical or autopsy material is referred to or whether the author is recording merely the lymphadenopathy encountered when the patient was first seen or that which may have occurred later in the course of the illness.

Of our 213 cases, 174 have been carefully followed to date or to death. The distribution of enlarged lymph nodes as observed clinically is seen in Table 2.

TABLE 2. *Lymphadenopathy During the Course of Hodgkin's Granuloma in 174 Cases.*

| LYMPHADENOPATHY | NO. OF CASES |
|---|---|
| Cervical | 149 |
| Axillary | 112 |
| Mediastinal | 90 |
| Inguinal | 73 |
| Abdominal | 33 |
| Epitrochlear | 10 |

In 14 patients there were no palpable lymph nodes except in the cervical area at any time during life. Of these, 1 is alive and apparently well twenty-four years after the onset of his disease. The course of the other 13 cases did not differ materially from the general average. In 2 cases, the enlarged nodes were limited to one inguinal region. One of these patients died after four years; the other is alive, following a groin dissection, five years after onset. In 2 cases only were the lymph nodes apparently limited to the mediastinum. It is of some interest that each of these patients died within a month of his first symptom, dyspnea.

In some cases, a varying degree of cervical lymphadenopathy was present over a long period of

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This is the fifth of a series of seven papers covering the various aspects of Hodgkin's disease.

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time without causing any symptoms. A sudden increase in the size of the nodes then caused the patient to seek medical advice. It is impossible to say in these cases whether the condition was true Hodgkin's granuloma from the onset, whether the initial lymph nodes were merely inflammatory or whether they represented one of the precursor pathologic conditions, such as Hodgkin's paragranuloma, or giant-follicle lymphoma. In any event, the persistence of cervical lymph nodes in adults, even if they vary greatly in size from time to time, demands much more serious attention than is often accorded it. This matter has already been referred to under "initial symptomatology" in one of the previous papers of this series. One further case may be cited here.

E. H. P. (H 29–831), a 46-year-old man, was admitted to the hospital on June 25, 1929. His mother had died of tuberculosis and his father of "carcinoma." The past history was unimportant.

In 1919, the patient noticed a small, nontender lump in the right axilla. This varied greatly in size, at times being as large as a walnut and at others no larger than a bean. Five years later this mass was excised by his family physician, but no further treatment was advocated and no pathological study was made. The patient continued to feel well until 1928, when he noted increasing constipation and some pain, unrelated to defecation, in the region of the coccyx. Early in January, 1929, the pain became worse and "spread throughout the rectum." The constipation continued, and in the next 6 months he lost 18 pounds, although his appetite remained good.

Physical examination on admission showed marked tenderness over the symphysis pubis and the lower part of the sacrum. There were several large, firm, freely movable lymph nodes in the right axilla. X-ray films of the gastrointestinal tract and lungs showed no abnormalities, but did reveal a destructive process in the sacrum "probably due to Hodgkin's disease." Rectal examination was negative. A node was removed from the right axilla and showed the typical lesion of Hodgkin's granuloma.

In the course of the next 2 months, 1200r was given over the sacrum and pelvic region, but the patient continued to lose weight rapidly and died on August 11. No autopsy was obtained.

The nature of the cervical lymphadenopathy that continued, with remissions and relapses, from 1919 to 1929 in this case is, of course, uncertain, but it is our belief that, in adults, notably enlarged lymph nodes, unless associated with obvious infection, are almost always tuberculous or cancerous, and one cannot help speculating what the course of the disease would have been had a radical dissection of the axilla, followed by intensive x-ray therapy, been carried out in 1919.

In other cases, proved tuberculous adenitis has preceded by months or years the development of Hodgkin's granuloma in the same region. This sequence of events was seen in 6 of these 213 cases.

Desjardins and Ford[1] have stressed the relation of infected teeth and tonsils to the appearance of Hodgkin's granuloma in the cervical region, but the great frequency of such pyogenic infections, the comparative rarity of Hodgkin's granuloma of the tonsil, the frequency of involvement of the posterior triangle in that disease and the relative frequency of the involvement of the axillary and inguinal lymph nodes seem to argue against any direct etiologic relation. It is perhaps likelier that acute upper respiratory or oral infections simply light up an already existing dormant disease or bring to the attention of the patient lymph nodes already enlarged but otherwise symptomless.

Axillary and inguinal lymph nodes due to Hodgkin's granuloma are more likely to be painful from their position than those in the neck, but otherwise they do not differ in their characteristics. Epitrochlear nodes, although traditionally associated with secondary syphilis and often secondary to obscure infections of the hand, are sufficiently often due to Hodgkin's granuloma to demand serious attention. Indeed, it may safely be said that any lymph node materially enlarged over a period of time and unassociated with infection in an adult should receive a biopsy. On the other hand, it is extremely unusual for Hodgkin's granuloma to occur without the presence of superficial lymph nodes at some time or another during its course. We entirely agree with the following statement by Baker and Mann:[2]

> Hodgkin's disease of deep structures unassociated with superficial glandular enlargement is rare. In view of the frequency with which a diagnosis of Hodgkin's disease is made in cases of mediastinal tumor, of splenomegaly and so forth, a diagnosis often proved wrong by subsequent events, we deprecate the diagnosis of Hodgkin's disease in the absence of histological evidence obtained by biopsy of superficial lymph glands. If no superficial glands are obtainable during the course of the disease, the case is probably not one of Hodgkin's disease.

The obvious exceptions to this general rule serve only to accentuate its importance.

### *Hodgkin's Sarcoma*

In Hodgkin's sarcoma, the presence of enlarged superficial lymph nodes when the patient first comes to the physician's attention is by no means so frequent as it is in Hodgkin's granuloma. Indeed, in nearly half of our cases such peripheral initial lymphadenopathy was absent (Table 3).

TABLE 3. *Initial Lymphadenopathy in 32 Cases of Hodgkin's Sarcoma.*

| LYMPHADENOPATHY | No. of CASES |
|---|---|
| Cervical | 10 |
| Axillary | 5 |
| Inguinal | 3 |
| None | 14 |

Peripheral lymphadenopathy is usually although not invariably present during the course of Hodgkin's sarcoma (Table 4). The very generalized peripheral lymphadenopathy so frequent in Hodgkin's granuloma is seldom seen. Mediastinal lymph nodes

are involved in approximately one third of the cases, although massive involvement is rare. It should be recalled that the disease frequently starts in the

TABLE 4. *Lymphadenopathy During the Course of Hodgkin's Sarcoma in 32 Cases.*

| LYMPHADENOPATHY | NO. OF CASES |
|---|---|
| Cervical | 21 |
| Axillary | 19 |
| Inguinal | 15 |
| Mediastinal | 10 |
| Abdominal | 9 |
| Epitrochlear | 6 |

retroperitoneal lymph nodes, and these, of course, are not readily felt during life.

## TONSILS AND NASOPHARYNX

### *Hodgkin's Paragranuloma*

Involvement of the tonsils and nasopharynx does not exist in Hodgkin's paragranuloma.

### *Hodgkin's Granuloma*

Hodgkin's granuloma rarely involves either the tonsils or the nasopharynx. In but 6 of our 213 cases was there such involvement. In 1 there was a large, translucent mass in the posterior pharynx. In the remaining 5, a tonsil was involved unilaterally by a mass described as whitish or translucent. The surface was occasionally ulcerated. In each case, the involvement of the tonsil occurred early in the disease and was almost invariably accompanied by notable cervical lymphadenopathy. This fact reflects the rapidity with which this form of the disease advances. New and Childrey,[3] in a comprehensive study of certain tumors of the tonsils and pharynx, found that 59 per cent of the patients had enlarged cervical lymph nodes when first seen.

The serious nature of this condition and the ease with which, by contrast, it may be confused with more innocent affections of the throat require more than passing notice.

The age of the patients in this series varied greatly, the youngest one being seven and the oldest seventy-nine. The median was forty-four years. The symptoms were varied, including cough, dysphagia, persistent sore throat and hemoptysis. Five patients died of generalized Hodgkin's granuloma in less than two years from the time that the involvement of the tonsil or pharynx was noted. The remaining patient was, in a sense, more fortunate.

W. W. (P 8212), a 79-year-old man, noticed in May, 1934, a soreness in the left side of the throat, together with an enlargement of the left tonsil. Gargles and hot applications did not seem beneficial, and he was admitted to the hospital on June 26, 1934. Physical examination at that time revealed a well developed and well nourished elderly man. There was a firm, opalescent tumor, measuring 5 by 3 by 3 cm., arising from the left tonsil. There was no cervical lymphadenopathy, and the remainder of the physical examination was essentially normal for a man of his age.

The red-cell count was 4,060,000, the hemoglobin 80 per cent, and the white-cell count 10,600, with a normal differential count. X-ray examination failed to reveal any disease in the heart, lungs or bones.

The tumor was removed as completely as possible, and radium seeds were implanted in the underlying fossa, a total of 528 mc. hr. being given. In addition, during the next 2 months a total of 1200 r (250-Kv. machine) was given to the left cervical region. There was no recurrence of the disease, and the patient died of heart failure in January, 1940, more than 5 years after onset.

It is admittedly rare to see such a localized lesion, yet the cases illustrate the necessity of careful inquiry into the causes of sore throat in elderly persons and the advisability of employing to the fullest extent all therapeutic measures, even in the face of an apparently hopeless situation.

### *Hodgkin's Sarcoma*

Involvement of the tonsils and nasopharynx by Hodgkin's sarcoma is not rare; it occurred in 11 per cent of our cases. In 3 of these the tonsil was involved, and in 1 the palate and antrum. The most frequent initial symptoms are localized pain, nasal obstruction, tumor in the throat and sore throat. In addition, during the course of the disease, loss of weight is almost invariable, and dyspnea, sometimes due to nasal obstruction, is not infrequent.

The tumor is highly invasive and destructive, and patients afflicted with this type of involvement live but a short time. None of those in this series lived over three years after onset. The tumors of the tonsil have, in our experience, been extremely large and ulcerated, and although they usually have responded well to initial irradiation recurrence has been rapid and later irradiation has had but little effect. In 1 case, there was a bluish tumor over the hard palate that rapidly extended, destroying the surrounding bone and filling the right antrum. In spite of irradiation, there was subsequent extension into the right nostril, with death ensuing shortly.

The following case may be cited as an example of this type of infiltration.

P. G. (HH 24–806), a 45-year-old man, was admitted on June 27, 1924, with a chief complaint of sore throat. In the previous April he had noticed a growth in the throat and felt generally weak.

Physical examination on entry showed a large, sloughing tumor involving the right tonsil and extending up into the nasopharynx. In addition, there were several enlarged, nontender lymph nodes in the right side of the neck. Eight seeds of 1 mc. each were inserted into the tumor tissue. Within a week the growth had disappeared to a great extent, but 9 months later the left tonsil became enlarged to such an extent that it filled almost the entire pharynx. Four 1.5-mc. seeds were inserted into the tumor, with good local results, but there was a residual enlargement of the lymph nodes in the left side of the neck. A moderate amount of x-ray therapy was directed toward these, with but little effect.

The patient was constantly tired. The nares were almost completely obstructed by the tumor, and there was a troublesome productive cough and a severe sore throat. In addition, there was a distressing generalized headache. He developed marked exophthalmos and ptosis of the left eye and, in spite of x-ray therapy, died 3 years after the first symptom.

*Autopsy.* Post-mortem examination showed Hodgkin's sarcoma involving the right tonsil, with direct extension to the nasopharynx and the sphenoidal sinus and involvement of the pituitary gland, the right orbit, the right temporal bone and the adjacent dura.

## Liver and Spleen

### *Hodgkin's Paragranuloma*

In 21 per cent of our cases of Hodgkin's paragranuloma, enlargement of the spleen was noted during life, and progressive enlargement of this organ has been, in our experience, an ominous sign. Enlargement of the liver practically never occurs.

### *Hodgkin's Granuloma*

Both the liver and spleen are frequently enlarged in Hodgkin's granuloma. From a study of the reported cases, Wallhauser[4] came to the conclusion that hepatomegaly was present in about 50 per cent of the cases and splenomegaly in approximately 70 per cent. Uddströmer[5] found slightly lower figures — 36 per cent for the liver and 63 per cent for the spleen.

In our own cases followed to date or to death, the liver was enlarged in 30 per cent and the spleen in 56 per cent. It is probable that these figures are too low.

Only rarely does either organ reach massive size. In spite of the frequency with which these organs are involved, symptoms referable to them are surprisingly rare. Ascites was present in but 11 of our 62 cases with hepatomegaly, and jaundice occurred in only 6. Splenomegaly occasionally reaches massive proportions without causing any symptoms whatever, but it is not infrequent for patients in whom the spleen is greatly enlarged to complain of a dragging sensation in the left side of the abdomen, and occasionally an enlarged spleen causes acute pain, particularly if there is an associated perisplenitis.

It is well recognized that the size of the spleen may increase greatly in the presence of fever, and indeed it may be palpable only during periods of pyrexia. It is not so well known that an enlarged spleen may diminish in size without any treatment whatever. All in all, enlargement of these organs, although frequent, does not appear to have great clinical importance, except in so far as it indicates the generalized nature of this condition.

### *Hodgkin's Sarcoma*

In Hodgkin's sarcoma, enlargement of the liver and spleen occurred — always coincidentally — in 38 per cent of our cases. Rarely, however, is there great enlargement of either organ at autopsy, and their involvement does not appear to contribute materially to one's knowledge of the future course in any given case. In 2 cases the liver extended to the level of the umbilicus or lower, and in 1 the spleen reached nearly to the iliac crest.

## Serous Cavities

### *Hodgkin's Paragranuloma*

Involvement of the serous cavities does not occur in Hodgkin's paragranuloma.

### *Hodgkin's Granuloma*

In Hodgkin's granuloma, pleurisy with effusion is frequent. Evidence of fluid within the pleural cavity was found in 35 of such of our cases as had been followed to date or to death. In 8 of these, the fluid was present bilaterally. In the great majority of cases it appears to be dependent on involvement of the mediastinal nodes; much more rarely it is secondary to granulomatous lesions of the pleura. Versé[6] was of the same opinion. Occasionally it is tuberculous in origin.

In 6 of our cases, the effusion was bloody; in 1, it was chylous and apparently due to tuberculous invasion of the thoracic duct; and in 1 a colon-bacillus empyema had developed as a result of a fistulous tract that perforated the diaphragm and connected the colon with the pleural cavity through a series of necrotic nodes. All other effusions were serous.

The amount may be small, and the fluid may disappear after one or two taps and appropriate x-ray therapy to the mediastinum. Oftener, unfortunately, the amount of fluid is large and repeated thoracenteses are required for adequate relief. Under these circumstances, the eventual subsidence of the effusion depends very largely on the response of the hilar and mediastinal nodes to radiation therapy. In this connection, one point is perhaps worthy of passing comment. The diaphragm is frequently elevated in the presence of a mediastinal tumor, and it may remain high after the subsidence of the mass so that by cursory examination there are still signs highly suggestive of fluid. In 1 of our cases, death resulted from a lack of recognition of these facts. Four years previously, the patient had had a mediastinal tumor and a massive effusion on the left. Under x-ray therapy these had subsided, but the left diaphragm had remained greatly elevated. Under the impression that fluid still existed, a needle had been introduced into the chest by a physician unfamiliar with the patient's history; the diaphragm was perforated, and death resulted from hemorrhage from a lacerated spleen.

In our experience, pleural effusions may develop at any time during the course of the disease although they are usually late. They do not appear to have any definite bearing on the prognosis.

Baker and Mann[2] describe spontaneous pneumothorax. This complication we have not seen.

It is generally agreed that the peritoneum is but rarely implicated directly, and likewise ascites is a rather infrequent complication.[5] We have found clinical evidence of ascites in only 5 per cent of our

cases, and in all but 1 of these the complication was terminal and was followed by death within a month or six weeks. In this single case, ascites was present intermittently for a year prior to exitus, but it appeared to be dependent on cardiac failure rather than on granulomatous involvement of the peritoneum. In another case, a massive ascites developed terminally and was shown at autopsy to have been due to alcoholic cirrhosis of the liver. It is always well to remember that a patient with Hodgkin's granuloma may in addition have some other major disease. Our own failure to recognize this fact has, in one or two cases, been unfortunate. Ascites should be regarded as of serious import unless occasioned by remediable factors.

We have encountered pericardial effusion during life in only 2 cases. In each, the fluid was hemorrhagic and death ensued shortly after its clinical recognition.

*Hodgkin's Sarcoma*

Pleurisy with effusion is also not infrequent in Hodgkin's sarcoma. In our own series, it occurred in 7 (22 per cent) of the cases during life. In 6 of these, the fluid was grossly bloody. This is in sharp contrast to the character of the pleural fluid of Hodgkin's granuloma, which, as we have said, is usually serous. In Hodgkin's sarcoma, the effusion is usually associated with involvement of the lungs. In several cases, however, there was no evidence during life of involvement of either the lungs or the mediastinal lymph nodes. It is not improbable that in these cases there was direct implication of the pleura itself by the neoplastic process. The effusions, whether sanguineous, serous or purulent, have invariably been extremely large in amount and not seldom have required frequent thoracenteses.

Ascites occurred in only 2 cases.

We have never seen pericarditis with effusion.

## Nervous System

*Hodgkin's Paragranuloma*

Involvement of the nervous system is never seen in Hodgkin's paragranuloma.

*Hodgkin's Granuloma*

In Hodgkin's granuloma, signs and symptoms referable to the cord or peripheral nerves are not unusual. Actual invasion of the brain substance or cord is extremely rare.[7,8]

Cortical manifestations are infrequent. Johnsson[8] found only 8 cases exhibiting cerebral symptoms among 37 that had some involvement of the nervous system. Epileptiform seizures are, however, occasionally seen, and appear in practically all cases to be due to invasion of the dura. So far as we are aware, there is only 1 case reported in the literature in which a granulomatous lesion was found in the substance of the cortex. Von Hecker and Fischer[9] describe in some detail the case of a thirty-two-year-old man suffering from what appeared clinically to be widespread Hodgkin's disease. A few days before death he had several epileptiform seizures, followed by deep coma. At autopsy there was found in the region of the centrum semiovale a cherry-sized granulomatous focus that showed a histologic picture extremely suggestive of Hodgkin's granuloma. Even in this case, however, some question may be raised whether the cortical lesion was actually Hodgkin's granuloma, for earlier biopsy of an axillary lymph node had shown small round-cell sarcoma, and according to the authors themselves many of the involved organs failed to show a clear-cut histologic picture. Johnsson has been erroneously quoted in the literature as describing cortical lesions, but he specifically points out that in no case other than that of von Hecker and Fischer[9] was there any histologic evidence of involvement of the brain substance. Among our patients, there was 1 who exhibited terminally signs of increased intracranial pressure, choked disks, rotatory nystagmus, progressive coma and death. Unfortunately, no autopsy was obtained. Terminal headache, convulsions and coma are frequent; their cause is obscure.

Symptoms referable to the spinal cord are relatively frequent.[3, 8, 10, 11] One patient died in coma following the rapid development of a meningitis.

W. A. (BCH 346957), a 35-year-old man, was admitted on November 22, 1916. In 1911 he noticed enlargement of the lymph nodes in the left side of the neck and the left axilla. For the next 5 years, the swellings gradually increased in size, particularly during the winter months. In the month of admission, he noticed gradual swelling of the abdomen. His general condition remained good.

Physical examination on admission showed many firm lymph nodes in the left side of the neck and the left axilla. There were signs of fluid in the right pleural cavity, and ascites was also present. The veins over the lower abdomen were enlarged. The temperature, pulse and respirations were normal. The red-cell count was 5,400,000, the hemoglobin 75 per cent, and the white-cell count 3500; with 50 per cent neutrophils, 15 per cent lymphocytes and 35 per cent monocytes. The platelets were normal. The patient was comfortable and up and about the ward.

Six weeks after admission, the patient suddenly screamed and fell to the floor. Thereafter there was deepening coma, and the temperature rose to 105°F. There were no pupillary changes and no paralysis. Death occurred on January 5, 1917.

*Autopsy.* Post-mortem examination showed Hodgkin's granuloma of the cervical and axillary lymph nodes and of the spleen, central necrosis and regeneration of the liver, ascites, bloody fluid in the pericardial sac and acute meningitis. In the foramen magnum and beneath the right temporal lobe there was 75 cc. of brownish mucopurulent fluid. The pial vessels were slightly injected. The brain, pons, medulla and pituitary were normal, except that on the pia over the cortex, basal ganglia and dorsal cord microscopical examination showed a moderate amount of seropurulent exudate. Cultures of the brain and cord yielded a beta-hemolytic streptococcus. No origin of the meningitis was found.

Although actual granulomatous lesions arising within the substance of the cord are extremely rare,

if indeed they exist, neurologic symptoms may be produced in various ways:

In the first place, epidural or subdural granulomatous deposits may surround and press on the cord.

Secondly, there may be pressure from lesions arising in the vertebras or from collapse of vertebral bodies that have been destroyed by the disease. In 92 per cent of Weil's[10] cases, the symptoms could be traced to dural lesions or those in the spine itself. Sudden death has been reported from dislocation of the diseased spine and severance of the cervical cord.[12] In our series, the evidence points to bone lesions as being the most frequent source of cord symptoms.

Thirdly, there may be compression or actual invasion of the vessels and lymphatics of the cord by tumor from the adjacent lymph nodes. Weil[10] in particular has stressed this type of involvement. He writes:

> The mechanism of the myelopathy . . . can easily be explained by the mechanical obstruction of blood vessels and lymphatics supplying the spinal cord through the lymphogranulomatous tissue, either within the intervertebral foramina or outside the spinal canal. . . . It can easily be understood that the interruption or diminution of vascular supply of the spinal cord, if continued over a longer [*sic*] period of time, will produce a diffuse myelomalacia, which will be the more severe the more spinal arteries are involved.

Fourthly, there may be a meningitis.[3]

And, finally, there may be a toxic myelitis of uncertain nature. Allen and Mercer[11] in particular have stressed this origin of the spinal symptoms. Gordon[13] and others demonstrated that the intracerebral inoculation of rabbits with emulsions of tissue derived from cases of Hodgkin's granuloma produced signs of ataxia, muscular spasms and paralysis. Examination of the cord in such animals reveals few definite lesions. The fact that in experimental animals and in some clinical cases there is a marked disparity between the severity of the clinical manifestations and the paucity of the findings on anatomic or histologic examination raises the interesting speculation whether, in man, certain cases of paralysis may not be due to some ill defined toxin derived from the granulomatous tissue. The possibility cannot be denied, yet extremely careful study at autopsy would be necessary to rule out invasion of the dura or epidural space and lymph nodes pressing on afferent blood vessels. It has recently been demonstrated that the Gordon phenomenon is due to the presence of eosinophils,[14] and in this connection it is worthy of note that in both the cases described by Allen and Mercer[11] there was an eosinophilia, amounting in 1 case to 78 per cent.

Nine of our 174 cases, on which we have complete clinical data, showed evidence of paralysis of the legs. In 7, the paralysis was flaccid; in 2, it was spastic. In all 9 cases there was diminution or absence of tactile sensation, and in all there was some disturbance of the rectal and vesical sphincters. In all, the point of origin appeared to be in the dorsal segments. In Weil's[10] series, the dorsal region was involved in 80 per cent, the cervical in 16 per cent, and the lumbosacral in 4 per cent. Weil regarded paralysis as a late and almost invariably fatal complication. In over 80 per cent of his collected cases the patients died within three months after the appearance of the neurologic symptoms, and none survived more than a year after the onset of the paralysis. That the prognosis is not always so grave is attested by the fact that 3 of our 9 patients survived more than a year after the paresis or paralysis had set in, and 1 was alive and in comparatively good health four years later.

J. C. (HJ 1–30), a 35-year-old policeman, in the early part of 1930 noted enlarged painless lymph nodes in the left side of the neck. A biopsy at that time showed the typical picture of Hodgkin's granuloma. X-ray therapy was instituted, and the nodes promptly subsided. In 1933, the patient developed a mediastinal tumor and a left-sided pleurisy with effusion. Under x-ray treatment and after several chest taps, the mediastinal mass subsided and the fluid disappeared. He remained in fairly good health.

Early in July, 1935, the patient suddenly developed weakness and numbness of both legs. A few days later, he became completely paralyzed from the waist down. There was no pain. He had some difficulty in starting the urinary stream, but no incontinence. The abdominal and cremasteric reflexes were absent. The knee jerks and ankle jerks were equal and hyperactive. There was a bilateral Babiński sign and sustained clonus. No movement could be made from the waist down. Tactile sensation was markedly diminished, and pain sensation was absent below a line parallel with the nipples anteriorly and the midscapula region posteriorly. Lumbar puncture showed evidence of complete block. The initial pressure was equivalent to 160 mm. of water. There was no rise on jugular pressure. Coughing or straining caused a rise to 310 mm. The spinal fluid was clear and colorless, with 2 lymphocytes per cubic millimeter. The Pandy test was strongly positive. No gold-sol curve was done.

X-ray studies of the spine revealed no definite abnormalities. There were numerous small, shotty lymph nodes in each side of the neck, each axilla and each groin. The heart appeared to be normal. The left diaphragm was markedly elevated. The abdomen was normal. There was no fever.

High-voltage x-ray therapy was immediately begun over the dorsal spine. Within 3 weeks there was less difficulty in passing urine and tactile sensation began to return. By August 8, approximately 1 month after the onset of the paralysis, the patient was able to move his legs slightly. By the end of August, the improvement was marked, and he was able to move his legs in all directions, though he was unable to bear any weight on them. There were still bilateral Babinski signs and ankle clonus. From that time on, improvement was slow but continued. By June, 1936, a year after the paralysis set in, he was able to walk with crutches, and by October of the same year he could walk without assistance. His general condition was good. Sensation had become normal, and the only abnormal neurologic finding was that both knee jerks and ankle jerks were hyperactive. From July, 1935, to October, 1937, he had received a total of 4300 r (250-kv. machine) to the dorsal spine. In September, 1937, he developed a broad band of herpes zoster corresponding to the distribution of the fourth thoracic spinal nerve on the right. After 3 weeks this cleared, leaving a broad scar, as herpes usually does when due to Hodgkin's granuloma.

The patient was able to return to duty as a sergeant in the police force, and although his legs were somewhat weak, he remained active until his death by accident in May, 1939, nearly 3 years after the onset of the paralysis.

No autopsy was performed in this case, and the cause of the symptoms must therefore remain a matter of conjecture. It is probable, however, that

granulomatous tissue had extended from the para-aortic nodes through the intervertebral foramens to surround and compress the cord, and this supposition is somewhat strengthened by the development of the herpetic lesion in the upper dorsal region, for it has been suggested by many that herpes in Hodgkin's granuloma is due to pressure on the spinal roots by granulomatous tissue.

In this case, no gold-sol curve was done on the spinal fluid, nor have we seen any such determinations reported in the literature. In other cases in this series, however, in which there was paralysis associated with Hodgkin's disease or some other form of lymphoma the spinal fluid has shown a midzone curve suggestive of syphilis or early multiple sclerosis. Under x-ray therapy, the curve has usually flattened out or shown a tendency to less marked midzone rises.

In 5 of the other cases in this series in which there was paralysis of the legs, there was marked destruction of the thoracic and lumbar vertebras, and it seems reasonable to assume that the paralysis was due either to pressure on the cord from collapsed vertebras or to pressure from surrounding granulomatous lesions that had coincidentally invaded the vertebras. There was, however, no autopsy confirmation of this supposition. In 2 cases, paralysis was secondary to meningitis. In one of these, a pyocyaneus-bacillus meningitis apparently originated from a fistulous tract extending through necrotic lymph nodes from the intestine to the spinal canal. In the second, there was a torula meningitis of uncertain origin.

Symptoms referable to peripheral nerves are frequent. Abdominal pain often seems to originate in this fashion, perhaps owing to pressure on dorsal roots. Less often there is pain in the face, neck, arms or legs. Herpes zoster is a not infrequent complication and usually leaves a scar after its subsidence. Exophthalmos and enophthalmos are occasionally encountered. Rarely the cranial nerves are implicated.[15]

### *Hodgkin's Sarcoma*

Involvement of the central nervous system in Hodgkin's sarcoma is not frequent. We have seen 3 cases involving the cerebellum, but unfortunately the post-mortem examination in each case was limited to the head.

In view of the rarity of this condition it may not be amiss to include one of the case histories.

P. L. (BCH 1049224), a 65-year-old Italian, was admitted on September 10, 1941, in an unconscious state. He had been well until March, 1941, when following a minor injury he became shaky and staggered while walking. These symptoms forced him to quit work about the end of July. They increased gradually during the ensuing months, and in early September his speech became thick and mumbly. In addition, he complained of difficulty in swallowing. At approximately the same time, the right eyelid tended to droop. He became stuporous and at times could not recognize his own family.

On admission, the patient was well developed and poorly nourished. The pupils were equal and reacted well. The corneal reflexes were bilaterally diminished, more so on the right. There was weakness of the right external rectus muscle so that the right eye could not be brought beyond the midline on looking to the right. There was ptosis of the left lid and bilateral horizontal nystagmus. The entire right side of the face was paralyzed. The gag reflex was absent, and the patient was barely able to swallow. His speech was dysarthric and somewhat nasal. There was no evidence of weakness of the extremities. Both the finger-to-nose and heel-to-knee tests were poorly executed. The biceps and triceps reflexes and ankle jerks were slightly weak. The abdominal reflex was absent, and there was no ankle clonus. The plantar reflex was absent on the right, and present on the left. There were no other notable abnormalities.

On lumbar puncture, the initial pressure was found to be equivalent to 60 mm. of water. The dynamics were delayed, and the final pressure was 0 after the removal of 10 cc. of fluid, which contained 40 lymphocytes per cubic millimeter and 189 mg. protein per 100 cc. The gold-sol curve was 0001233210. The Pandy reaction was ++. Examination of the peripheral blood showed no abnormalities.

The patient became progressively worse and more and more stuporous and died 8 months after the first symptoms.

*Autopsy.* Post-mortem examination showed that the pons, as viewed from the ventral aspect, was unusually broad, the right half being 0.4 cm. wider than the left. Horizontal sections disclosed a tumor mass occupying the white matter of the right cerebellar hemisphere, the right middle cerebral peduncle and the tegmentum of the pons and upper medulla on the right side. The tissue there was soft and gray, and was almost liquefied in the central portions. There was no sharp line of demarcation between the tumor tissue and the adjacent brain tissue. In the largest horizontal diameter the lesion measured 3.2 by 3.4 cm. The tumor extended posteriorly to reach the leptomeninges of the cerebellar cortex and medially to the fourth ventricle, which was distorted and almost obliterated by the enlargement of the right cerebellar hemisphere. The lateral and third ventricles were dilated to about twice normal size, and the aqueduct of Sylvius was also enlarged. A slight but definite cerebellar pressure cone had formed. The large arteries showed a slight amount of atherosclerosis. The leptomeninges and dura were not remarkable. The histologic features of the tumor were those of Hodgkin's sarcoma.

It is probable that the right sixth and seventh nerve palsies in this case were due to invasion or compression of the abducens and facial nuclei or of the intramedullary portions of these nerves. Right cerebellar ataxia appeared to be on the basis of destruction of the middle cerebellar peduncle and the right dentate nucleus. The nystagmus was best explained by involvement of the vestibular nuclei. The dysarthria and dysphagia were probably pseudobulbar.

In another case, there was clinical evidence of compression of the spinal cord in both the cervical and dorsal regions. The total protein was markedly elevated, and the gold-sol curve was 000012332. Autopsy showed that masses of tumor tissue had infiltrated between the vertebras and had surrounded the cord, resulting in marked depression of the fourth through seventh thoracic and the first through third dorsal nerves. In addition, the disease was widespread, involving the muscle of the thoracic wall, the para-aortic lymph nodes, the thalamus, the left cerebral cortex and the liver.

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# THE EFFECT OF THE PREDIABETIC STATE ON THE SURVIVAL OF THE FETUS AND THE BIRTH WEIGHT OF THE NEWBORN INFANT*

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ONE of the outstanding characteristics of infants born to diabetic mothers is a high fetal and neonatal mortality rate. In addition there occur in some infants born to diabetic mothers striking somatic and visceral changes, among which are an increased birth weight, cardiomegaly, hyperplasia of the islands of Langerhans, excessive extramedullary erythropoiesis, hyperplasia of the adrenal glands and an increase in the eosinophil elements of the anterior pituitary body.[1] Similar observations have been made on infants born to mothers who were not diabetic at the time of delivery but in later months or years developed signs and symptoms of diabetes.[2] Since all the mothers who have been studied thus far became diabetic during the childbearing period, — that is, under forty years of age, — it was considered desirable to extend the observations to infants born to mothers whose diabetes appeared after they had passed the fourth decade.

## SOURCE OF DATA

The files of the New Haven Hospital were searched for records of women who developed diabetes after forty years of age. The time of onset was determined by the history of the appearance of the first symptom or the detection of glycosuria and hyperglycemia. A history of a birth was acceptable only in case the age of the mother at the time of the birth of the infant and all its siblings could be determined. Infant deaths in this study include all cases listed as stillbirths and all infants dying in the first week of life. A birth weight was considered acceptable only in infants born in the New Haven Hospital. A control group of infant cases was obtained from the records of women admitted to the New Haven Hospital after the age of forty with diagnoses other than diabetes mellitus. Histories of births and birth weights in the control group were subjected to the same restrictions as were imposed on the diabetic group. A third group of infants born to obese but nondiabetic mothers was also studied in respect to their birth weights. The diagnosis of obesity was limited to women weighing two hundred pounds or more during a pregnancy or one hundred and seventy-five pounds or more when not pregnant but while still in the childbearing period.

## RESULTS

The mortality rate for infants born to mothers who subsequently became diabetic during or after the fifth decade of life has been compared to the rate among infants of nondiabetic mothers (Table 1). The mortality rate of 8.3 per cent for the prediabetic group is significantly higher than that of 2.0 per cent for the nondiabetic group. It is not supposed that the mortality rates are exact for either group of infants, since, in a history, deaths of infants are likelier to be overlooked than are surviving infants and some so-called "miscarriages" may have been prematurely born infants who failed to survive. It is believed, however, that any errors involved in obtaining true infant mortality rates from histories recorded several years later are equally distributed between the two groups of

TABLE 1. *The Mortality Rates among Infants Born to Nondiabetic and Prediabetic Mothers.*

| STATUS OF MOTHER | NO. OF MOTHERS | NO. OF BIRTHS | NO. OF INFANT DEATHS | MORTALITY RATE % | |
|---|---|---|---|---|---|
| Nondiabetic | 59 | 253 | 5 | 2.0 | 10.5* |
| Prediabetic | 57 | 264 | 22 | 8.3 | |

*Chi square.

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infants. The groups are comparable in that most of the infants were delivered between 1910 and 1930. Furthermore, as is shown later in Table 3, the distributions of births according to the ages of the mothers are almost identical for the prediabetic and nondiabetic groups.

The effect of the approaching onset of maternal diabetes on the survival of the fetus is demonstrated by the data in Table 2. The mortality was 15.8

TABLE 2. *The Effect of Approaching Maternal Diabetes on Infant Mortality Rates.*

| PERIOD OF ONSET OF DIABETES | NO. OF BIRTHS | NO. OF INFANT DEATHS | INFANT MORTALITY % | |
|---|---|---|---|---|
| 16 or more years | 201 | 12 | 6.0 | 6.2* |
| 15 or less years | 63 | 10 | 15.8 | |

*Chi square.

per cent among the infants born fifteen years or less before the onset of maternal diabetes. This is a significantly higher mortality than that of 6.0 per cent found for infants born sixteen years or more before the diabetic syndrome was diagnosed in the mothers.

It is a generally recognized fact that the newborn-infant mortality increases with the age of the mother. The data in Table 3 show the newborn infant mor-

TABLE 3. *Infant Mortality Rates according to Age of Mother at Time of Delivery.*

| AGE OF MOTHER | NO. OF BIRTHS | | INFANT MORTALITY | |
|---|---|---|---|---|
| | NONDIABETIC | PREDIABETIC | NONDIABETIC | PREDIABETIC |
| yr. | | | % | % |
| 16-20 | 16 | 30 | 0 | 3.3 |
| 21-30 | 145 | 146 | 3.4 | 5.5 |
| 31-40 | 88 | 87 | 0 | 10.3 |
| 41-45 | 4 | 4 | 0 | 100.0 |

tality rates according to the age of the mothers at the time of delivery. It is seen that the mortality rates among the infants of nondiabetic and prediabetic mothers are strikingly divergent when delivery occurs in the fourth and fifth decades of life. The absence of any increase in infant deaths in the nondiabetic group as compared with the marked increase in the prediabetic group that occurs in the latter half of the childbearing period suggests that maternal age is a negligible factor in the increasing newborn mortality that occurs as the onset of diabetes is approached in the mothers.

The data on the birth weights of infants born to prediabetic mothers are few, since the chances were small that a woman would enter the New Haven Hospital after the age of forty years with diabetes mellitus and would have been delivered in this hospital several years before. No infants who weighed less than 2500 gm. at birth and no twins were included. In Table 4, the average birth weight of 22 infants born to 16 prediabetic mothers is compared with the average birth weight of infants born to nondiabetic mothers. Determinations for sugar in the urine or for blood-sugar concentrations were made during the course of 20 of the 22 cases.

TABLE 4. *Comparison of Average Birth Weights of Infants of Nondiabetic and Prediabetic Mothers.*

| STATUS OF MOTHER | NO. OF MOTHERS | NO. OF INFANTS | AVERAGE BIRTH WEIGHT | STANDARD DEVIATION | STANDARD ERROR OF DIFFERENCE |
|---|---|---|---|---|---|
| | | | kg. | | |
| Nondiabetic | 40 | 112 | 3.53 | ±0.50 | |
| Prediabetic (total) | 16 | 22 | 4.15 | ±0.68 | 0.16 |
| Prediabetic (15 yr. or less before onset of diabetes) | 12 | 17 | 4.40 | ±0.55 | 0.14 |

Reducing substances were found in the urine of 3 mothers during pregnancy, but in 2 of these the fasting blood sugar was 87 mg. per 100 cc. in one and 89, 94 and 112 mg. in the other. The third mother had three urine examinations made during pregnancy, two of which failed to show the presence of reducing substances. None of the 16 mothers had signs or symptoms of diabetes at the time their infants were delivered. They all subsequently developed diabetes in the fifth or sixth decade of life. Their average age at the onset of diabetes was 45.4 years. Eight of the 16 mothers had passed the menopause before their diabetes became manifest. The 22 infants with but one exception were delivered before the mothers attained the age of forty years. All but 3 of the 22 infants were born six years or more before the onset of maternal diabetes.

The average birth weight of the 22 infants born to 16 prediabetic mothers was 4.15 kg.; that of the 17 infants who were born fifteen years or less before the onset of diabetes in their mothers was 4.40 kg. The average weights of both these groups are significantly higher than the average birth weight of 3.53 kg. for the nondiabetic group. Three of the 22 infants born to prediabetic mothers weighed more than 5.0 kg. at birth; 6 weighed over 4.5 kg. and 15 weighed 4.0 kg. or more. These incidences are approximately two hundred, twenty-seven and seven times greater than the expected ratio of births in these respective weight categories.[3, 4]

Ten of the 16 mothers in the prediabetic group reported in Table 4 attained a weight of 175 pounds either during the childbearing period or subsequent to it. Because obesity is one of the frequent characteristics of women developing diabetes in later life, and because it seemed possible that the maternal obesity was a factor in the increased birth weights, a study was made of the birth weights of infants born to women who were obese at the time of pregnancy (Table 5). No significant difference was found between the average birth weight of the infants in the obese group and those in the nondiabetic group.

## Comment

The nature of the factor or factors responsible for the increased newborn mortality and increased birth weights of infants born to prediabetic mothers remains unknown. Presumably the primary factors are the same as those that are responsible for the high mortality and increased birth weight of infants born to mothers who already have developed diabetes. Recent studies by Smith, Smith and Hurwitz[5] suggest that fetal and neonatal deaths in diabetic pregnancies are related to a premature increase in estrogen and progestin production by the placenta, followed by a decreased production of these same steroids at an earlier time in the gestation period than is to be expected. White and Hunt[6] have urged the treatment of diabetic pregnant mothers with estrogen and progesterone on the basis of an observed imbalance of the sex hormones in pregnancies terminating fatally for the fetus or newborn infant. The striking changes in the islands of Langerhans, adrenal glands, gonads and anterior hypophysis of some infants born to diabetic mothers are additional evidence that endocrine factors are almost certainly involved in their production. The fact that all these dramatic changes can be found in the infant several years before there is any evidence of diabetes in the mother[2] suggests that additional knowledge of the etiology of diabetes is to be gained by further study of the factors responsible for the increased mortality rate and the somatic and visceral changes seen in infants born to diabetic mothers.

Table 5. *Comparison of Average Birth Weights of Infants of Nondiabetic Mothers and Obese Mothers.*

| Status of Mother | No. of Mothers | No. of Infants | Average Birth Weight | Standard Deviation |
|---|---|---|---|---|
| | | | kg. | |
| Obese | 17 | 21 | 3.60 | ±0.54 |
| Nondiabetic | 40 | 112 | 3.53 | ±0.50 |

The causes of death in many fetuses and newborn infants are still unexplained or poorly understood. The results of the present study indicate that a certain percentage of these deaths are now to be accounted for on the basis of factors associated with the subsequent development of diabetes in the mothers. The fact that fetal and neonatal deaths are increased for several years before the appearance of diabetes in the mothers points toward a high degree of sensitivity on the part of the human fetus to the factors involved, whether or not they are endocrine.

The data presented in this study indicate a new explanation for the excessive birth weight of some fetuses. The number of infants weighing over 4 kg. at birth whose excessive birth weight can be accounted for on the basis of a prediabetic state cannot be judged from the few cases reported here. The fact that 11 of the 12 mothers who had babies born to them fifteen years or less before the onset of maternal diabetes were delivered of infants weighing 4 kg. or more suggests that women developing diabetes past the childbearing period are recruited almost wholly from 5 to 7 per cent of mothers who give birth to babies weighing over 4 kg.

## Conclusions

The fetal and neonatal mortality rates and the average birth weight are increased among infants born to mothers who subsequently manifest diabetes mellitus, even though the latter do not develop the disease until after forty years of age.

The fetal and neonatal mortality rates increase as the onset of maternal diabetes is approached.

Maternal obesity is not a factor in the increased average birth weight of infants born to prediabetic mothers who become diabetic after the age of forty.

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# MEDICAL PROGRESS

## THE PARENTERAL USE OF VITAMIN PREPARATIONS*

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IN 1943 the National Research Council[1] published what it considered to be adequate daily allowances of the better known vitamins. Although the recommended amounts have been attacked as too large from the viewpoint of minimum requirements, these allowances, which admittedly include a factor of safety of at least 30 per cent,[2] provide physicians with standards concerning the vitamins a normal person should ingest. The field of parenteral vitamin therapy, by contrast, appears to be one of hopeless confusion. Parenteral vitamin preparations of all types are, literally and figuratively, a drug on the market, but information concerning their proper use is indeed scarce. What vitamins should be given parenterally? How much vitamin is lost in the urine after an intravenous injection? What are the needs of the patient who is ill enough to require parenteral administration of vitamins? In this review, an attempt is made to answer some of these questions in the hope of making available some guiding principles to the physician who is at times forced to resort to parenteral vitamin therapy. Because the available evidence is limited, and often indirect or equivocal, conclusions reached and dosages suggested must at best be considered roughly approximate and highly tentative. Emphasis in this discussion is placed on the needs of the average medical or surgical patient whose nutrition must be maintained but who, for some reason or other, requires the parenteral administration of vitamins. No attempt is made to discuss the treatment of specific and advanced deficiency diseases, such as pellagra, scurvy and so forth.

Vitamins, like other foodstuffs, are best taken by mouth. Parenteral administration is, however, justified for certain patients, who include the following: those unable or forbidden to take any food by mouth; those suffering from a defect in intestinal absorption; those who are so acutely deficient in vitamins that the delay of intestinal absorption must be circumvented; those who require fairly large doses of vitamins but suffer from a disorder that oral preparations might aggravate (a physician might prefer, for example, to treat a patient with ulcerative colitis with parenteral vitamin B complex rather than to give large doses of brewer's yeast by mouth); and those unable or unwilling to ingest a specific vitamin preparation that is indicated.

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The kind and amount of vitamins needed by patients in the above categories naturally vary from case to case, for some of the patients will be able to eat and absorb at least a part of their vitamin requirements. The dosages suggested in this review, however, are intended for the patient whose total needs for the vitamin under discussion must be supplied by parenteral means. In computing these needs, one must allow for the daily requirement as well as the amount necessary to build up vitamin stores depleted by illness or deficient diet. Except when laboratory facilities are available for testing a patient's vitamin reserve, the amount of vitamin needed to replenish his stores must be estimated. For any one vitamin, this amount presumably lies somewhere between the normal requirements and the needs of a patient frankly deficient in that particular vitamin. It might be argued that vitamins are safe: Why not give huge doses and be sure that the patient's needs are covered? Besides the expense involved in such a practice, it is difficult to justify nonspecific and grossly excessive vitamin therapy merely on the grounds that vitamins are relatively nontoxic substances.

In estimating the vitamins needed by any patient, his whole nutrition should be considered as a unit. One cannot consider the vitamin and the caloric intakes independently; nor does intensive therapy with a single vitamin appear to be judicious in the average case. The interrelation of vitamin needs and caloric intake is illustrated by the person who is subjected to complete starvation. He is not liable to develop an acute vitamin deficiency. Should he, however, terminate a prolonged fast by ingesting large quantities of sugar, symptoms and signs of various deficiencies might develop in rapid order. The reason for this sequence of events is that vitamins take an active part in metabolic processes. In starvation, metabolism is depressed, relatively few calories are burnt up, and the need for vitamins is correspondingly reduced. When calories are supplied to the body by sugar, however, the depleted vitamin stores are rapidly consumed, and frank manifestations of deficiency appear. In view of these facts, the patient who has had a calorically deficient intake may have better vitamin stores than the one who has taken a calorically adequate but vitamin-poor diet. Similarly, a man subsisting on parenteral nutrition is more in need of vitamins if his caloric intake is adequate than if it is deficient. Obviously, one should aim in such a case at an

adequate supply of calories fortified with the necessary vitamins.

The necessity of a balanced vitamin therapy, particularly with respect to the vitamin B complex, is still a matter of debate. Yet it seems likely that a patient who is receiving all his nutrition parenterally requires not only thiamine chloride but also other fractions of the vitamin B complex, unless good evidence is available that the stores of these other fractions are adequate. As a matter of fact, the clinical impression is strong that the intensive administration of a single component of the vitamin B complex to a patient whose stores of vitamin B complex are low accentuates the needs for the other fractions.[3–6] Animal experiments both confirm[7, 8] and negate[9] the clinical impression that intensive therapy with a single vitamin may be harmful. By far the greater part of the evidence indicates, however, that parenteral vitamin injections that are given for the purpose of maintaining nutrition should never consist of a single vitamin. Only in case a specific indication for treatment with a single vitamin exists — the vitamin K deficiency of obstructive jaundice, for example — does it seem warranted to inject one particular vitamin.

Methods for the quantitation of vitamins in the tissues, body fluids and excreta of man vary tremendously, both in reliability and in technic. Not infrequently the results obtained from bioassay and chemical analysis do not coincide. Consequently, values for vitamin concentrations reproduced in this text from the literature are subject to change when more specific methods are developed, although the figures given for such well studied vitamins as thiamine chloride and ascorbic acid show quite satisfactory correlation irrespective of the method of determination.

For purposes of clarity, two terms that are used throughout this review, "saturation" and "biosynthesis," should be defined.

*Saturation.* In searching for a laboratory test of vitamin deficiency, investigators have administered a vitamin in specific amounts — the "load" — and have then determined the quantity of that vitamin excreted in the urine during a certain time period. According to the theory behind this test, a deficient subject excretes only a minute fraction of the test dose. As treatment with the appropriate vitamin is given, the subject excretes a gradually increasing proportion of the test dose until the amount excreted reaches a limit beyond which it will not rise, even though the subject continues to receive intensive vitamin therapy. At this point, he is considered to be saturated; that is, his body is considered to have stored as much of the vitamin as it can possibly hold, and any extra vitamin given is in large part destroyed or excreted in the urine. There is no evidence that a patient has to be saturated before his vitamin stores can be considered optimum; a much smaller quantity probably suffices for normal function.[10]

*Biosynthesis.* Certain organisms in the intestinal tract of animals and man, particularly the coliform bacteria,[11] can synthesize various vitamins. This process is referred to as intestinal biosynthesis.

## Thiamine Chloride

Thiamine chloride (vitamin $B_1$) is a water-soluble substance that is present in the blood both as free thiamine and as a phosphorylated compound, diphosphothiamine. The latter, also known as cocarboxylase, appears to be the physiologically active form of vitamin $B_1$[12] and is found in tissues and the cellular elements of the blood.[13] Free thiamine, which constitutes a small fraction of the blood's total thiamine content, is chiefly present in plasma.[13, 14] The average blood values[12–17] are as follows:

| | |
|---|---|
| Total thiamine | 4–10 microgm. per 100 cc. whole blood |
| Diphosphothiamine (chiefly in white cells and red cells) | 3–9 microgm. per 100 cc. whole blood |
| Free thiamine (chiefly in plasma) | 0.5–2.0 microgm. per 100 cc. plasma |

The concentration of thiamine in the tissues of the human body is about ten to twenty times that of whole blood, the total vitamin $B_1$ content of a normal man averaging about 25 mg.[3, 18] When illness and poor nutrition beset a patient, the tissue stores of thiamine may be drastically reduced.[3]

Solutions containing pure thiamine are suitable for subcutaneous or intravenous injection. When so given, the vitamin is apparently phosphorylated rapidly in such organs as the liver and the kidneys[12, 19] and is in part used in metabolic processes. Some is stored in the tissues, some is excreted in the urine, and insignificant amounts are lost in the feces and sweat.[12, 20–23] Actually, the absolute amount that can be measured as having been stored in the tissues is extremely small and limited[12, 18, 20, 24]; and the amount lost in the urine may be but a small fraction of the dose given, even if some possible metabolites of vitamin $B_1$ are taken into account.[13] It follows that considerable thiamine undergoes processes of metabolism or destruction that cannot be followed at present. Some light is shed on this problem, however, by studies using thiamine tagged with radioactive sulfur.[25] When such thiamine is given intramuscularly for four days to a human subject, 61 per cent of the tagged vitamin is recovered from the urine and 11 per cent from the feces in the ten days following the first injection. These studies also show that a sizable proportion of the thiamine excreted in the urine after vitamin $B_1$ is given parenterally is not derived from the injected dose but apparently is stored thiamine that is displaced from the body when more vitamin $B_1$ is administered.

Since the metabolism of vitamin $B_1$, particularly the question of destruction in the body,[26] is an un-

certain issue, the thiamine excreted in the urine is not necessarily the amount "left over" after metabolic and storage needs are satisfied. Nevertheless, a considerable body of opinion[6, 21] claims that the urinary excretion of vitamin $B_1$, after a specific test dose is given, is a good index of a patient's nutrition with respect to thiamine chloride. This appears to be particularly true if small test doses are given. A deficient subject, for example, has been found to excrete 2 to 6 per cent of a subcutaneous dose of 1 mg. of vitamin $B_1$ within twenty-four hours; whereas a subject with good stores excretes over 20 and often 50 per cent of such a test dose.[27, 28] Urine collected for a four-hour period after a subcutaneous dose contains most of the thiamine excreted in response to the injection; hence, after 1 mg. of vitamin $B_1$ subcutaneously, the four-hour urine in deficient subjects contains about 30 to 70 microgm., in normal subjects about 200 microgm., and in saturated subjects 500 to 700 microgm.[29, 30] These figures do not differ greatly from the average results obtained after oral or intravenous dosage. Three hours after an oral dose of 1 mg., about 65 microgm. is excreted by deficient and about 200 microgm. by saturated subjects.[24] An intravenous dose of 1 mg. of thiamine chloride in normal subjects is followed by an excretion of 100 to 200 microgm. in the first half hour, but the four-hour total is again in the vicinity of 15 to 25 per cent of the test dose.[3, 17]

Although oral test doses of 5 mg. of vitamin $B_1$ have been used,[18, 30] the parenteral administration of such a large dose has not found much favor as a diagnostic test for thiamine deficiency on the grounds that large doses "flood" the blood stream and are excreted by the kidney irrespective of the subject's needs, thus masking the difference between normal and deficient subjects.[19, 31, 32] In one series, an oral test dose of 5 mg. led to the excretion of 13 per cent in twenty-four hours in normal subjects, but 25 per cent of a similar intravenous dose appeared in the urine within four hours, and an intravenous injection of 30 mg. led to a 50 per cent excretion.[31] In deficient subjects, 12 per cent of an intravenous dose of 5 mg. and 40 per cent of an intravenous dose of 30 mg. were found in the four-hour urine samples. According to Borson,[19] the loss of thiamine in the urine following an intravenous injection of the vitamin occurs chiefly during the first hour and is of the following order of magnitude:

| DOSE OF THIAMINE mg. | URINARY EXCRETION % |
|---|---|
| 3 | 15 |
| 7 | 20 |
| 10 | 30 |
| 30 | 50 |
| 50 | 80 |

Gorham et al.[13] recovered between 411 and 1530 microgm. in the twenty-four-hour urine of normal subjects after 5 mg. of vitamin $B_1$ had been given intravenously. If the vitamin is given subcutaneously in large doses, its excretion in the urine during a three-hour period may be roughly similar to the findings after intravenous injection: 10 mg. of thiamine given subcutaneously is followed by a 20 per cent excretion, and 50 mg. by a 26 per cent excretion.[33]

Although the urinary output of thiamine after an intravenous dose may occasionally be small (only 2.8 per cent one hour after 15 mg. intravenously[18]), it seems fair to conclude that the parenteral administration of thiamine in doses over 3 mg. may be attended by an apparent urinary loss of 15 to 30 per cent, with increasing percentages attending higher doses. This loss, however, tends to be near the lower end of the range in deficient patients and probably far above 30 per cent in those who are saturated.

It is theoretically possible that the urinary excretion of thiamine is slightly less after subcutaneous administration or after a slow intravenous infusion than after an intravenous dose given during the course of half a minute. Caution must, however, be exercised in estimating the effectiveness of adding thiamine to an intravenous infusion. Early in his studies with the fractions of the vitamin B complex, Cowgill[34] showed that these substances can be washed out by diuresis. It was subsequently shown that the diuresis that attends thyrotoxicosis may carry with it considerable quantities of thiamine, even though the blood level of vitamin $B_1$ is low in this disease.[16, 19] When a mercurial diuretic is given, the ensuing diuresis may increase the excretion of injected thiamine to 60 per cent of the dose given.[12] The fact that diuresis can affect thiamine excretion profoundly has led to the suggestion that this vitamin is a nonthreshold substance,[19] and a renal-clearance study indicates that an extensive tubular resorption of thiamine does not take place.[14] Consequently, if an intravenous infusion is of such a composition, or if it is given at such a rate that diuresis is evoked, an increased amount of any thiamine given with the infusion is presumably lost in the urine.

*Requirements.* Estimates of the minimum requirement of thiamine for the normal adult person vary from 0.2[22] to 0.6 mg. per 1000 calories.[29] No benefit, however, is said to obtain from ingesting more than 1 mg. for each 1000 calories of food.[28] If one is guided by the more generous estimates of the needs of a normal man, a patient who receives 1500 calories per day, whether by mouth or by vein, should get about 1 mg. of vitamin $B_1$ daily. His disease, however, may or may not alter the thiamine requirements. In exercise, which may be comparable to disease in that the metabolic rate is elevated, the vitamin $B_1$ needs rise with the caloric requirements, but apparently the requirement of thiamine per calorie is not increased.[22] It is also stated that the evidence for an increased require-

ment of thiamine in fever is at present not conclusive.[35] In dogs, dinitrophenol raises the basal metabolic rate and produces some fever, but apparently does not increase the need for vitamin B complex.[36] On the other hand, thyrotoxicosis may increase the daily requirement two and a half times,[37, 38] and a daily dose of 10 to 20 mg. of vitamin $B_1$ is recommended in this disease.[16] This increased requirement in hyperthyroidism is probably due to an increased caloric consumption, to diuresis, to unknown factors and perhaps to hepatic dysfunction, which may cause the phosphorylation of vitamin $B_1$ to be impaired.[12, 39] It is probably safest to consider that the needs for thiamine are increased in disease,[22] and that a requirement of 1 mg. per 1000 calories be arbitrarily chosen. Allowing for a 25 per cent loss in the urine, a patient unable to ingest food but presumably with normal stores of thiamine — a case of acute appendicitis and peritonitis, for example — should therefore receive 3 mg. of parenteral vitamin $B_1$ a day if he is given about 2000 calories a day by means of intravenous infusions.

Unfortunately most patients who require parenteral administration of thiamine do not have normal stores of this vitamin. Of all the vitamins, the body seems to have least capacity to store thiamine chloride, evidences of deficiency at times appearing within a few days after a nonsaturated normal subject has taken a thiamine-free diet.[23] Longer intervals, ranging between twenty and forty days, are usually necessary, however, before a normal subject on a thiamine-free diet develops severely depleted stores[25] or unequivocal signs of deficiency.[22, 40] Even saturation by means of excessive doses of vitamin $B_1$ will not ensure storage for more than two or three weeks.[24, 27, 31] Patients, of course, do not subsist on a thiamine-free diet, but the quantity of vitamin $B_1$ actually available to their metabolic needs is often limited for a variety of reasons. Sometimes the nature of the illness causes the patient to consume a diet limited in its content of the vitamin B complex, although the caloric intake is adequate by dint of taking bland, starch foods. Or the patient may have consumed adequate quantities of thiamine, but its absorption may have been impeded by gastric anacidity, excessive intake of antacids or a diarrheal state of some type.[41, 42] Finally, as has been mentioned, fever, hyperthyroidism, renal function or hepatic function frequently influences the patient's metabolism and storage of vitamin $B_1$.

Unless facilities are available for measuring the thiamine content of the urine, the estimation of a patient's thiamine stores is practically impossible. A probable range, however, can be proposed. In a subject on a thiamine-deficient diet for twenty days, an oral dose of 5 mg. of vitamin $B_1$ daily for six days was necessary before a normal response to a saturation test was observed.[18] A patient with a low thiamine excretion in the urine following a saturation test responded normally after 10 mg. of vitamin $B_1$ had been given daily for five days.[3] In another study, roughly 15 mg. by mouth daily for ten days was apparently not quite enough to correct the biochemical abnormalities in a severely depleted subject.[29] A total dose of 100 to 125 mg. was necessary to saturate deficient patients with alcoholic neuritis, but this dosage may have exceeded the total deficit, since liver function was obviously affected in these subjects.[19] Spies[43] recommends 25 mg. daily for patients with beriberi. In thyrotoxic patients, 10 mg. of vitamin $B_1$ given parenterally twice daily for six to ten days elevated the thiamine content of the blood to normal levels.[16] These figures for the needs of subjects with definite thiamine deficiency, taken in conjunction with the fact that the total vitamin $B_1$ content of man averages 25 mg.,[18] suggest that the patient who has no clinical signs of thiamine deficiency but whose stores have presumably been depleted during his illness needs about 50 mg. of thiamine in addition to his daily requirements. For patients who have to receive this supplement parenterally, 10 mg. a day for ten days should suffice to cover daily needs, repletion of stores and urinary losses. After ten days, the dosage can be decreased to the amount estimated as the daily requirement.

In many patients, the suggested dosages will probably be excessive; in others, particularly, if thyrotoxicosis, fever or diuresis complicates the picture, they may be insufficient. There seems to be little indication, however, for injecting huge doses of thiamine chloride unless frank and acute symptoms of deficiency are present. Repeated doses of 100 mg. daily, for example, presumably lead to a large urinary loss, which, if the patient is saturated, may approximate the dose injected. To be sure, it has been suggested that the metabolic exchanges in which thiamine participates are impaired under certain conditions, such as shock, anoxia and irradiation sickness,[44, 45] and that large doses of vitamin B complex may in part correct the abnormality. The efficacy of large parenteral doses of thiamine, niacinamide or pyridoxin in irradiation sickness or analogous disorders remains, however, to be proved. It seems advisable, when possible, to ensure proper nutrition before starting radiation therapy.[46]

One rare complication of parenteral thiamine therapy is sensitization to the vitamin. In the reported cases,[47, 48] the following train of events is usual: repeated and large doses of vitamin $B_1$ are injected into a patient; a period without therapy follows during which sensitivity presumably develops; resumption of parenteral thiamine therapy is thereupon followed by acute allergic symptoms, which may include respiratory distress and collapse. The fact that many of these patients received huge

doses of thiamine constitutes another argument against injecting vitamin $B_1$ in amounts far in excess of what is needed for adequate nutrition.

Biosynthesis of thiamine chloride apparently occurs in the human intestine,[20, 49] but its implication in human nutrition is debatable.[40, 50] The fact that 50 mg. of thiamine given by retention enema increases the urinary excretion of the vitamin has been advanced as evidence that the vitamin $B_1$ biosynthesized in the human colon is available for man's nutritive needs.[40] This evidence has been attacked on the grounds that 50 mg. is far in excess of the amount usually produced in the intestine (the average fecal vitamin $B_1$ content in man is 150 to 350 microgm. per day[49]) and that most of the thiamine in the feces is present as unabsorbable cocarboxylase.[50] In view of the well known tendency of enemas to regurgitate into the ileum, it is also questionable whether absorption after a retention enema proves that this occurred in the large bowel. From the viewpoint of the patient who requires parenteral nourishment, however, the debate is somewhat academic. Intestinal disease per se may affect biosynthesis in an unknown manner. If, as is likely, the patient is not able to eat, his gut lacks the fiber and starches that appear to stimulate thiamine production by the intestinal organisms.[49] Finally, many of the patients receiving vitamins parenterally may have received or are receiving sulfonamides, which depress the organisms chiefly responsible for biosynthesis.[11, 40, 51] It seems that the vagaries of disease, the cessation of oral feeding and the intestinal disinfectants used before and with surgery tend to eliminate intestinal biosynthesis as an important factor in maintaining the necessary supply of thiamine.

## Riboflavin

Riboflavin is a water-soluble fraction of the vitamin B complex. In human blood, it is chiefly present in the red cells, in concentrations ranging between 35 and 50 microgm. per 100 cc. of whole blood.[52, 53] In human tissues, between 2 and 13 microgm. of riboflavin are present per gram of tissue.[3, 52] Man's bodily stores of riboflavin thus appear to be about four to six times his thiamine stores, a ratio that also holds true in the rat.[26]

Like other pure fractions of the vitamin B complex, solutions containing pure riboflavin can be injected subcutaneously or intravenously. The intravenous route was used by Axelrod et al.[54] in carrying out a series of saturation tests with 200 microgm. of riboflavin per kilogram (10 mg. riboflavin for a subject weighing 110 pounds). In the twenty-four hours subsequent to the injection, 10 to 63 per cent of the test dose was recovered from the urine, the response of normal subjects apparently not differing from that of patients presumably deficient in riboflavin. With a larger dose — 400 microgm. per kilogram — 72 per cent was excreted in the urine during the first twenty-four hours. These results led Axelrod and his collaborators to decide that the saturation test was not useful in diagnosing riboflavin deficiency. Subsequently, however, it was shown that test doses employing 1 mg. intravenously,[3, 55] 2 mg. subcutaneously[56] or 16 microgm. per kilogram (a total of about 1 mg.) intramuscularly[57] led to urinary excretions that showed good correlation with the subject's nutritional status. The deficient subjects, in general, excreted below 25 per cent of the test dose in the four hours immediately following the injection; the excretion of normal subjects varied between 25 and 75 per cent, whereas saturated individuals excreted 70 to 100 per cent. No difference was apparent between oral and intramuscular test doses when a small dose (16 micrograms per kilogram) was used.[57] The difference between the results of Axelrod et al. and those of the other investigators has been ascribed to the large parenteral doses used by the former.[55, 58] Riboflavin, like thiamine, is apparently retained according to the needs of the patient when given in small parenteral doses, but when larger doses (5 mg. or more) are injected, the urinary loss is also affected by renal function, by the extent to which the blood stream is loaded and by other variable factors.

*Requirement.* Keys,[58] in 1944, wrote that the "estimation of the riboflavin requirement of man and the diagnosis of riboflavin deficiency are in a peculiarly unsatisfactory state." The truth of this statement can be appreciated when one realizes that some nutritional surveys continue to accept cheilosis and corneal vascularization as specific evidences of riboflavin deficiency, although careful studies[58–60] suggest that such a view is incorrect.[61, 62] Since the signs of riboflavin deficiency are the object of debate, the daily requirements are also uncertain. The National Research Council[1] proposed 2.7 mg. for a moderately active adult male of 70 kilograms (0.9 mg. per 1000 calories). On the other hand, a diet offering only 0.31 mg. of riboflavin per 1000 calories produced no physiologic handicaps, although it may have lowered the body's reserves of the vitamin.[58] Others believe that the minimum requirement to maintain adequate stores is above 0.5 mg. of riboflavin per 1000 calories.[56] The allowance for an ill patient might therefore be placed at 1 mg. per 1000 calories. On this basis, a daily parenteral dose of 3 to 4 mg. would both satisfy a patient's daily needs and allow for a 25 to 30 per cent loss in the urine.

The body's stores of riboflavin appear to be less rapidly depleted than those of thiamine. All the tissues of 3 chronically ill patients studied by Ferrebee and Weissman[3] were found to contain extremely low levels of vitamin $B_1$, but the riboflavin levels were below normal in only 1 case, a tuber-

culous patient who had been maintained on parenteral glucose and saline infusions for two weeks. Normal subjects, whose stores had been well supplied, consumed a diet restricted in riboflavin for thirty days before the urinary excretion after a saturation test was significantly decreased.[56, 58] Conversely, in markedly deficient subjects, a total riboflavin dosage of 40 to 50 mg., given daily in small oral doses, was sufficient to bring about saturation as judged from the fact that the daily urinary excretions of the vitamin attained a constant, high plateau.[63] Eleven milligrams of riboflavin daily for a week appeared to be more than enough to "supercharge" subjects who had had no clinical evidence of riboflavin deficiency but who had subsisted on a restricted regimen (0.31 mg. riboflavin per 1000 calories) for five months.[58] From these figures, it appears that a patient who has been ill or who has had a restricted riboflavin intake for less than two weeks requires no more riboflavin parenterally than that given to cover his daily requirement. For patients who have been subjected to possible riboflavin deprivation for longer periods, 10 mg. for five days should compensate for any depleted stores that may exist, unless the metabolism of riboflavin is radically altered by disease.

The interrelation of riboflavin with other foodstuffs is of some theoretical importance. On the basis of animal experiments, it has been suggested that the absorption and utilization of riboflavin is impaired in thiamine deficiency.[64] In man, such a relation is not demonstrable, and the explanation has been offered that the apparent interrelation between vitamin $B_1$ and riboflavin may be a nonspecific phenomenon: when tissues are broken down and weight is lost (due to thiamine deficiency, in this case), riboflavin is liberated and excreted as an unused product of tissue catabolism.[3] In line with this suggestion is the fact that riboflavin excretion in laboratory animals and in man is increased during periods of protein depletion or starvation.[65] After periods of protein depletion, the hepatic stores of riboflavin are decreased; with adequate protein supplies, the hepatic riboflavin content is increased.[66] Hence, in animals, protein deposition in the liver appears to be necessary to retain riboflavin in this organ, which is a major site of riboflavin storage in man (liver tissue contains 13 microgm. of riboflavin per gram[3]). The administration of adequate amino acids[67] to a patient requiring parenteral nourishment may therefore promote the storage of any riboflavin that is given.

Small injections of thiamine chloride may temporarily increase the urinary output of riboflavin in normal human subjects, but this observation seems to be of little nutritional significance since large doses of vitamin $B_1$ given for one to ten weeks do not produce any clinical or biochemical evidence of riboflavin lack.[68]

The biosynthesis of riboflavin appears to occur in man.[69] Although succinylsulfathiazole does not decrease the fecal riboflavin output,[69] the small amounts of riboflavin produced, the question of their availability[70] and the unpredictable effects of disease on intestinal biosynthesis argue that one should not rely on this source in estimating a patient's riboflavin needs.

*(To be concluded)*

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# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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## CASE 31391

### PRESENTATION OF CASE

*First admission.* A sixty-three-year-old man was admitted to the hospital complaining of severe headache.

For a number of years he had had episodes of weakness and vertigo, without loss of consciousness. An hour before admission he complained of pain in the back of the neck. Fifteen minutes later he was found unconscious and breathing heavily. In forty-five minutes he regained consciousness and on admission complained of suboccipital and neck pain.

Six months before admission the patient had undergone a perineal prostatectomy and recovered uneventfully. At that time the blood pressure was 130 systolic, 70 diastolic, and no cardiac murmurs were heard.

On physical examination the neck was stiff. The pupils reacted to light and accommodation. The tendon reflexes were more marked on the right than on the left. The plantar responses were normal. There was no disturbance of speech. Scattered retinal hemorrhages were seen about the right disk. During examination the patient vomited several times.

On lumbar puncture grossly bloody spinal fluid under increased pressure was withdrawn, with temporary relief of the headache. The spinal-fluid Wassermann test was positive; the blood Hinton test was positive, and the Wassermann doubtful. A week after admission, the number of red cells in the spinal fluid had decreased and the fluid had become xanthochromic. A week before discharge, the spinal-fluid Wassermann test was negative.

The patient was discharged six weeks after admission.

*Second admission* (three months later). The patient again complained of headache and was readmitted. The pain occurred daily, usually being present when the patient awoke, continuing for about an hour and then gradually subsiding. It was referred to the occipital region and radiated down both sides of the neck and occasionally to the forehead. During such an attack the neck was sore but not stiff. There had been no visual disturbances.

The fundi were normal. A soft diastolic murmur was heard over the tricuspid area. The blood pressure was 130 systolic, 78 diastolic. The tendon reflexes were still more active on the right than on the left. The plantar responses were normal.

The blood Hinton reaction was positive, and the Wassermann negative.

He was discharged improved after four weeks.

*Third admission* (one year later). The patient was readmitted because of fatigue and slight exertional dyspnea of several months' duration and moderately acute dyspnea and orthopnea for one day.

On entry the blood pressure was 142 systolic, 55 diastolic. The heart was enlarged to the left anterior axillary line. A loud, harsh systolic murmur was heard along the left border of the sternum, with a loud, blowing diastolic murmur over the same area. Numerous moist rales were heard at the lung bases. A Corrigan type of pulse and capillary pulsations were noted.

An x-ray examination of the chest showed that the heart was moderately enlarged in the region of the left ventricle, with a transverse diameter of 18.5 cm. and an internal chest diameter of 32.2 cm. The aorta was tortuous and moderately dilated. The lung fields were clear. The diaphragm was smooth and showed a normal excursion.

An electrocardiogram showed regular rhythm at a rate of 55, a PR interval of 0.18 second, sagging $ST_1$ and $ST_2$, diphasic $T_1$, inverted $T_2$, upright $T_3$, low $T_4$ and moderate left-axis deviation. The QRS complexes were slightly blurred, measuring up to 0.10 mm. The blood Hinton and Wassermann reactions were both positive.

He was discharged on the ninth hospital day.

*Final admission* (one year later). One week before readmission the patient, at that time sixty-six years old, noticed pain high in the epigastrium radiating upward to the base of the neck and anteriorly just above the sternal notch. He perspired profusely, but there was no change in pulse, respirations or blood pressure. This attack lasted about thirty minutes, and the pain was relieved by nitroglycerin. The following night two similar attacks occurred, but they were less severe than the first; these were also relieved by nitroglycerin. Twenty-four hours later a fourth attack occurred, and at that time a physician found epigastric tenderness. The heart beat was less vigorous than previously, but the pulse was slow and regular. The following day he felt well and went to work. Five days later, in the evening, pain again developed in the suprasternal notch, but without accompanying pain in the epigastrium. A short time later numbness appeared in the left foot and gradually spread up the left leg. This numbness was soon followed by excruciating pain in the same distribution. Numbness later appeared in the right foot, but lasted only thirty minutes and was not followed by pain.

On admission the patient was in great pain, perspiring profusely. The heart beat was regular, at a

*On leave of absence.

rate of 50, and the sounds were of fair quality, with a harsh systolic murmur in the aortic area. The left lower extremity was white and paralyzed, with no sensation or reflexes. Neither femoral pulse could be palpated.

The blood pressure was 120 systolic, 60 diastolic on the right; and 130 systolic, 60 diastolic on the left.

Shortly after arrival at the hospital the patient gasped and expired within a few minutes.

## Differential Diagnosis

Dr. Paul D. White: This patient showed evidence of intracranial bleeding. Subarachnoid hemorrhage could have explained the situation, and I was going to ask Dr. Kubik, if he were here, about the various etiologic factors in the production of an intracranial aneurysm that might rupture and produce such symptoms; perhaps Dr. Castleman can answer the question. Bleeding from the ordinary congenital aneurysm in the circle of Willis, with which we have of late become somewhat familiar, has in my experience given rise oftener to headache than to pain in the back of the neck. Here we have a sixty-three-year old man with evidence of syphilis. Can syphilis cause an aneurysm of the circle of Willis, such as we see in young persons with congenital weakness of the vascular wall? Since this man probably had central-nervous-system syphilis, which is essentially vascular syphilis, there need not have been an actual aneurysm but rather a diffuse involvement of the blood vessels of the meninges, a kind of internal hemorrhagic pachymeningitis, of which one of the causes is syphilis. I believe that is likelier than rupture of an aneurysm, especially in view of the fact that the symptoms continued in somewhat the same fashion in later periods. I speak of this now because I shall leave this part of the picture shortly, becoming involved with other lesions.

At the second hospital admission there was evidence of the beginning of what, from the sequence of events, probably was involvement of the heart in the syphilitic process, namely, the development of slight aortic regurgitation. The diastolic murmur in the tricuspid area was undoubtedly an aortic diastolic murmur, heard at the lower end of the sternum much better than over the aortic area, which is not infrequently our experience. Therefore we may suspect that this is evidence of aortitis, which had been there long before but had not previously involved the aortic ring. Whether all these attacks of headaches and soreness and other nervous disturbances were due to intracranial hemorrhages or thromboses it is difficult to say, but I think that they fit into the diagnosis of pachymeningitis, such as I have mentioned.

I want to interpolate between the second and third hospital admissions the question whether there is any record of antisyphilitic therapy. There is no mention of it here. That might have been a serious omission in therapy because of the evidence, in both the central nervous system and the cardiovascular system, that syphilis was there and should have been treated. It is in the early stages that one can sometimes stop the progress of aortitis.

Dr. Benjamin Castleman: He was given five doses of bismuth subsalicylate between the second and third admissions.

Dr. Reed Harwood: The physician who took care of him at that time decided not to continue the treatment; I do not know why.

Dr. White: Then the treatment was inadequate. There was progression of the cardiac involvement, and the onset of left ventricular failure, owing to the development of free aortic regurgitation.

Have we any x-ray films?

Dr. Milford D. Schulz: Apparently the films were lost except for one oblique view. There seems to be definite enlargement of the left ventricle.

Dr. White: Can you see the aorta?

Dr. Schulz: This is a left antero-oblique projection but the aortic shadow cannot be accurately traced.

Dr. White: The electrocardiogram is characteristic of the left ventricular strain that is found with aortic regurgitation. There is also an effect from digitalis, as shown by sagging of the ST segments. This may be a combined effect involving both.

Death occurred two years after the discovery of the cardiac involvement; this is a common duration of life following the diagnosis of cardiovascular syphilis in inadequately treated cases. It is difficult to tell whether nitroglycerin given earlier would have been strikingly helpful. The story sounds like one of prolonged attacks of angina pectoris coming at rest. The chief symptom is characteristic of angina pectoris, but it is of longer duration than usual. Its atypical character is quite in keeping not only with a slowly developing early arteriosclerotic coronary occlusion but also with aortitis with occlusion of the mouths of the coronary arteries.

I do not know the significance of the epigastric tenderness. I wonder if it was marked. Do you recall, Dr. Harwood?

Dr. Harwood: It was moderate.

Dr. White: This was probably due to gastric irritation. Was there an electrocardiogram taken during the period of the last few days before the final hospital admission?

Dr. Harwood: No.

Dr. White: There was probably no time for an electrocardiogram to have been taken when he came into the hospital because he lived only a few minutes.

Dr. Harwood: One was taken fifteen minutes before he died.

Dr. White: I should like to see it shortly.

This terminal complication is, of course, one of the chief problems of interest. The diastolic murmur

heard was less intense than it had been, owing to heart failure. "The left lower extremity was white and paralyzed, with no sensation or reflexes." That was the event that precipitated death, evidently an acute obstruction of the circulation of the legs, complete on the left and partial on the right. There are two explanations that are more probable than others. In the first place it could have been a massive embolus to the bifurcation of the aorta from an intracardiac thrombosis over the site of a myocardial infarct caused either by obstruction of a coronary artery because of an arteriosclerotic process or by occlusion of the ostium of the coronary artery by syphilitic aortitis, or possibly by both conditions. Or the answer could be an extensive dissection of the aorta occurring in stages, with or without final rupture. Death in either case could be ascribed to ventricular fibrillation rather than to terminal hemorrhage.

In summary, I believe that this case illustrates the evolution, rather late in life, of cardiovascular syphilis involving the cerebral circulation and aorta in particular, with the development of aortic regurgitation, left ventricular enlargement, dilatation and failure, and probably coronary ostial occlusion with myocardial infarction from that source rather than from a coincident coronary involvement; the terminal event was probably an embolic occlusion of the aortic bifurcation from intracardiac thrombosis, but possibly it was a progressive dissection of the aortic wall with occlusion of the coronary and left iliac arteries, followed by terminal cardiac tamponade from aortic rupture. I favor the former alternative. I do not recall having seen any cases of dissecting aneurysm with syphilitic aortitis as a background, but there are exceptions and this may be one of them. There remains the possibility of arteriosclerotic occlusion superimposed on syphilitic aortitis.

This final electrocardiogram (presented by Dr. Harwood), taken a few minutes before the patient died and about a week after the onset of pain, shows many ventricular premature beats in Leads 1 and 2, with bigeminal rhythm in these two leads. The rate is 65 or 70, with full-length conduction time (about 0.2 second); it should not be interpreted auriculoventricular block. There is slight left-axis deviation, with distinct sagging of the ST segments in Leads 1 and 2 and in Leads $CF_4$ and $CF_5$. The T waves are low throughout, especially in the limb, but they are upright in all three precordial leads (Leads $CF_2$, $CF_4$ and $CF_6$). There is still the probability that digitalis rather than acute myocardial infarction was responsible for at least a certain amount of the sagging of the ST segments. There is no marked elevation of the ST segments in any leads. Was he still getting digitalis?

DR. HARWOOD: Yes.

DR. WHITE: Whether the bigeminal rhythm can be ascribed to the digitalis is open to question. There was no indication clinically that he was toxic from digitalis?

DR. HARWOOD: No.

DR. WHITE: This final electrocardiogram clearly supports the diagnosis of a dissecting aortic aneurysm rather than that of myocardial infarction with embolic blocking at the aortic bifurcation; but I am not sure that it rules out the latter condition completely.

DR. HARWOOD: This case presented a problem of immediate therapy. The patient did not appear particularly ill. He had the most excruciating pain during the last two hours of his life. I had not been able to make up my mind what the matter was. The pain was above the sternal notch and passed deep into the sternum. It resulted in profuse perspiration. As soon as the pain disappeared the patient felt perfectly well. When the pain and ischemia of the left leg appeared, along with pain in the throat, I again thought, as I had once or twice during the previous week, of the possibility of dissecting aneurysm. On the other hand he had obtained some relief from nitroglycerin, and the possibility of myocardial infarction, perhaps from syphilitic involvement of the coronary arteries, could not be excluded. I talked with a surgeon who had had considerable experience with vascular occlusion of the lower extremities, and he agreed that we ought to get the patient into the hospital and make an attempt to remove the embolus if one was there. The patient did not survive long enough for the surgeon to see him.

### CLINICAL DIAGNOSES

Coronary thrombosis, with myocardial infarction.
Embolism to bifurcation of aorta.
Syphilitic aortitis.

### DR. WHITE'S DIAGNOSES

Coronary occlusion due to syphilitic obstruction of mouths of coronary arteries.
Occlusion of left iliac artery due to embolus at bifurcation of aorta from intracardiac thrombosis or to dissecting aortic aneurysm with terminal rupture and cardiac tamponade.

### ANATOMICAL DIAGNOSES

**Dissecting aortic aneurysm, with involvement of coronary mouths, occlusion of left femoral artery and rupture into pericardium.**
Hemopericardium and cardiac tamponade.
Cardiac infarction, left papillary muscle.
Cardiac hypertrophy.
Endocarditis, chronic rheumatic: aortic valve.

### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy showed a dissecting aortic aneurysm. The intimal tear occurred in the usual place, about 2 cm. above the aortic valve, and there was dissection proximally down to the

annulus fibrosus of the valve, completely surrounding the mouths of both coronary arteries. There was also dissection distally throughout the entire aorta down into the iliac arteries. The aneurysm occluded the left femoral artery by the contiguity of the raised intima on one side of the vessel against the opposite side of the vessel. There were also dissections for short distances into some of the major branches of the aorta, such as the renal, splenic and internal carotid arteries.

It seemed to us at the time of autopsy, and our sections confirmed it, that the hemorrhage in the dissecting aneurysm around the valve was older than that in the part of the dissecting channel above the tear. I believe, therefore, that the initial pain that the patient had a week before admission was due to the proximal dissection, which surrounded the mouths of the coronary vessels and gave him real anginal pain, the attacks during the following week being due to the blood clot around the coronary arteries. The final episode occurred when the dissection progressed distally to produce the peripheral occlusion. His death was due to an external rupture through the adventitia into the pericardium and to cardiac tamponade.

DR. HARWOOD: Could the aneurysm around the valve explain the disappearance of the diastolic murmur?

DR. WHITE: Was it striking?

DR. HARWOOD: Yes.

DR. CASTLEMAN: I do not know how to explain the murmurs. We found no evidence of syphilitic aortitis. There was no separation of the aortic cusps at the commissures to account for the regurgitation. In fact there was interadherence between adjacent cusps for a distance of 5 mm., such as one sees in rheumatic heart disease. There was no gross intimal scarring, and no microscopic evidence in the media suggestive of syphilitic aortitis. We cut many sections but have not been able to prove that the patient had syphilitic aortitis. Certainly, if he had it, it was minimal.

The heart weighed 700 gm. The base of the posterior papillary muscle in the left chamber was grayish to yellowish white, and microscopically it showed infarction of three or four weeks' duration — long before the first acute attack. In addition, the tip of the papillary muscle showed an infarction that would fit in with a week's duration. I suppose that the coronary circulation to the papillary muscle had been impaired before he had the aortic-wall dissection and that the hemorrhage around the coronary vessels produced anoxia of the heart to produce further damage to the tip of the papillary muscle. The main coronary arteries showed only moderate sclerotic changes.

DR. WHITE: Could you tell whether the aorta was dilated just above the aortic valve?

DR. CASTLEMAN: It was slightly dilated.

DR. WHITE: That might then have been from some process, such as senile weakness of the wall, other than syphilitic aortitis, with or without separation of the aortic cusps.

DR. CASTLEMAN: You mean senile ectasia?

DR. WHITE: Yes. What about the cerebral symptoms?

DR. CASTLEMAN: We were unable to obtain permission to examine the head.

DR. WHITE: Will you answer the question that I raised about the circle of Willis?

DR. CASTLEMAN: I do not believe that we have ever seen these symptoms due to syphilis, and I should feel that it was probably on the basis of a congenital aneurysm rather than of a pachymeningitis due to syphilis. Pain in the back of the neck is not at all infrequent.

DR. WHITE: The terminal electrocardiogram in this case pointed to the diagnosis of dissecting aortic aneurysm rather than to that of extensive myocardial infarction.

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## CASE 31392

### PRESENTATION OF CASE

*First admission.* A sixty-year-old woman entered the hospital complaining of pain and swelling in the legs of about ten years' duration. The pain came on when she stood for several hours at a time. Her health had otherwise been good. The blood pressure was 195 systolic, 110 diastolic. The left pupil was larger than the right. The heart and lungs were normal. Bilateral varicosities of the great saphenous system were ligated and injected. The patient recovered uneventfully and was discharged after two days.

*Final admission* (eleven years later). For five years after discharge the patient was followed in the Out Patient Department, other varices of the legs having been injected from time to time. Six years before readmission she presented a skin eruption of two months' duration. It consisted of red papules and nodules, with serpiginous outlines, 0.5 cm. in diameter, which were scattered over an area 5 by 7 cm. on the left elbow. Similar lesions were seen on the inner aspect of the thighs, with slight scaling in these locations, and on the right elbow. The Hinton and Wassermann tests were strongly positive. The patient denied venereal disease and gave no history of previous skin lesions. During the next three months the eruption subsided. The patient refused a lumbar puncture and permitted only a limited physical examination. The blood pressure was 150 systolic, 76 diastolic. The pupils were large and slightly irregular, but reacted to light and accommodation. The nasal septum was intact. There were no cardiac murmurs. The reflexes were normal. The patient kept no appointments for antisyphilitic therapy, and her case was considered to be closed.

Five years later, at the age of seventy-one, she returned to the hospital complaining of swelling of the legs. One and a half years before readmission an eruption appeared on the left forearm. Elsewhere she had been given potassium iodide and 1 gm. of intramuscular bismuth every two weeks for the four months before admission. A urinalysis done before her seventh bismuth injection showed no abnormalities, but shortly after it she noticed swelling of the legs and abdomen and pain in the back. She was somewhat nauseated but did not vomit. During the development of the swelling she gained 20 pounds in weight. She had had exertional dyspnea for about six months.

Physical examination revealed a fairly well developed and nourished woman, with rapid shallow respirations. There was marked pitting edema of the lower extremities extending up the back and the abdominal wall to the level of the xiphoid. The skin showed senile keratoses and areas of increased pigmentation on the legs. A diffuse, hazy scarring was seen in the center of the cornea of the left eye, and there were some fibrous strands over the lens of the right eye. The pupils reacted to light. The eye movements were normal, but right ptosis was present. The eyegrounds were normal. The superficial lymph nodes were not enlarged. There was tenderness to percussion over the left chest. The breasts were normal. Rales were heard throughout both lung fields. Resonance and breath sounds were decreased over both bases. The apex of the heart was percussed 9.5 cm. to the left of the midline. A blowing diastolic murmur was heard along the left sternal border. Rumbling presystolic and systolic murmurs were heard at the apex. The liver was palpable two fingerbreadths below the right costal margin. The spleen was not palpable. The abdomen was distended, and shifting dullness was elicited. Neurologic examination was negative.

The temperature was 97°F., the pulse 70, and the respirations 20. The blood pressure was 180 systolic, 90 diastolic.

Examination of the blood revealed a red-cell count of 4,000,000, with 13.5 gm. of hemoglobin, and a white-cell count of 5900, with 72 per cent neutrophils. The nonprotein nitrogen was 50 mg. per 100 cc., the fasting blood sugar 99 mg., and the protein 4.6 gm., with 2.0 gm. of albumin and 2.6 gm. of globulin. The carbon dioxide was 21.8 milliequiv. per liter, and the chloride 108 milliequiv. The urine had a specific gravity of 1.022 and gave a ++++ test for albumin; the sediment contained 5 red cells, 10 white cells and many hyaline casts per high-power field. Urine culture showed numerous colonies of colon bacillus. The nonprotein nitrogen rose steadily to 136 mg. per 100 cc., and the carbon dioxide fell to 14.6 milliequiv. per liter. The serum calcium was 7.7 mg. per 100 cc., and the phosphorus 5.7 mg. The serum sodium was 125.2 milliequiv. per liter, and the potassium 4.5 milliequiv. A cephalin flocculation test was ++ in twenty-four hours and +++ in forty-eight hours. A blood Hinton test was positive.

An x-ray film of the chest showed an abnormally high diaphragm, with a question of fluid in the abdomen. The heart was transverse in position. There was considerable increase in the lung markings. The pleural sinuses were obliterated. A lateral view showed no definite areas of consolidation.

The patient continued to complain of nausea. On the tenth hospital day the temperature rose to 102°F. and the white-cell count to 13,000, with 98 per cent neutrophils. Tenderness was elicited in the costovertebral angles and in both calves, being more marked on the right than on the left. Crackling rales were heard over the lungs, but there was no evidence of pleural effusion. Several plasma transfusions were given. An abdominal paracentesis was done, and 2800 cc. of turbid yellow fluid was withdrawn; the sediment showed no tumor cells.

On the eighteenth hospital day the cardiac murmurs became much louder than previously, with a questionable pericardial friction rub. The skin was cold and moist, and the blood pressure 88 systolic, 44 diastolic. The patient became irrational but also complained of epigastric pain and vomiting. As a plasma transfusion was being given she gasped and expired.

## Differential Diagnosis

Dr. Friedrich W. Klemperer: One thing seems to be certain about this patient; namely, she had syphilis. She came to the hospital because of a skin rash, which raised the suspicion of syphilis, and since that time she had been known to have persistently positive Wassermann and Hinton reactions. I do not believe that, in the presence of these persistent reactions, there can be any doubt about this patient's having syphilis. She developed an aortic diastolic murmur. In the presence of syphilis the most reasonable diagnosis would be syphilitic aortic regurgitation, but a presystolic and systolic mitral murmur were also heard. One might think of rheumatic heart disease involving the mitral and aortic valve. The heart disease, however, developed late in life, and we know that on previous occasions she had not had murmurs. Rheumatic heart disease does not develop as a rule at this time of life. The mitral murmur must be explained as an Austin Flint murmur, which is a mitral diastolic murmur heard in aortic regurgitation. It was probably due to dilatation of the left ventricle causing a relative stenosis of the mitral ring. Granted she had syphilitic aortic regurgitation, could the final illness be explained on the basis of failure due to this disease? If the heart failed because of syphilitic aortic regurgitation one would expect it to be extremely large. Physical examination does not bear that out; the heart was percussed 9.5 cm. to the left of the mid-

line. In the x-ray report nothing is said about the size. I should like to look at the films.

DR. MILFORD D. SCHULZ: The heart does not appear to be enlarged. I wonder about all these prominent lung markings. They are probably best explained by pulmonary edema, but lymphatic spread of metastatic carcinoma cannot be ruled out.

DR. KLEMPERER: So the evidence is against a failing syphilitic heart, and there must have been some other cause for her death. Could cardiac failure alone explain the terminal episode? Was cardiac failure present at all? I believe that cardiac failure was proved by the nature of the respirations, by the rales in the chest and by the large liver. I should like to know whether the neck veins were distended. I assume that they probably were, although nothing is said about them. Cardiac failure alone would not explain the rapid and marked rise in the nonprotein nitrogen. The nonprotein nitrogen may go up slightly in congestive failure, but not to that extent. The rest of the blood chemical findings could also be explained only on the basis of renal embarrassment. There was definite chloride retention, with corresponding reduction in the carbon dioxide content. The low total protein, with reduction in albumin, is consistent with renal disease and was a contributing cause of this patient's edema. The calcium was low, but this figure could have been accounted for by reduction in serum protein. I conclude that the patient had renal disease, as well as cardiac failure that was not fully accounted for by aortic regurgitation.

This patient was seventy-one years of age and was known to have had a blood pressure of 195 systolic, 110 diastolic, eleven years before admission, which means a long-standing hypertension, although a lower reading was obtained at one time. She would be likely to have had hypertensive and arteriosclerotic heart disease. It might be that this patient who had syphilitic involvement of the aorta also had involvement of the orifices of the coronary arteries. We might also consider the rare case of syphilitic involvement of the coronary arteries themselves. There is no evidence to make such a diagnosis, and in the absence of an electrocardiogram, I am inclined to explain the cardiac failure by the combination of aortic regurgitation and hypertensive and arteriosclerotic heart disease.

It remains to discuss the nature of the renal lesion. At the onset of the first symptoms of renal failure the patient was receiving bismuth. Bismuth is a heavy metal and, like mercury, is able to produce renal lesions that consist in degeneration and necrosis of the tubular epithelium. This condition is extremely rare in human beings and is known mostly from experimental studies in animals. Doses that are toxic in animals are many times the therapeutic doses. We do not know exactly how much bismuth she had been getting. I must assume that the 1 gm. given every two weeks refers to the compound and not to the metal, thus representing the conventional therapeutic dose of bismuth. This, however, remains uncertain because we know nothing about the solubility of the drug given. By and large not more than 200 mg. of metal are given weekly if the compound is insoluble. In the absence of direct information I must assume that the treatment was proper and, as such, not the cause of fatal nephritis. In addition, patients who have bismuth nephritis usually develop other toxic symptoms, such as a bismuth line and severe stomatitis. Renal failure as the only sign of bismuth poisoning is not known to me.

There are two kinds of renal disease thought to be due to syphilis. One, the nephrotic syndrome, usually appears early in the disease and rapidly improves on treatment. The other is the interstitial involvement of the kidneys described by Rich[1] in 1932. Little is known about the clinical signs and symptoms of the latter syndrome, and only a few cases have been described in which uremia was due to this kind of renal involvement. I believe that there is a definite possibility that the patient had this kind of interstitial nephritis, which is thought to be due to syphilis, but it seems more probable that she suffered from renal disease coincident with syphilis. She could possibly have had vascular nephritis, — she was known to have had long-standing hypertension, — but I doubt this, because at first she was able to concentrate urine well. That should not be possible in vascular nephritis of long standing. The patient's disease was rapidly progressive, whereas vascular renal lesions are usually slow in their development.

Did she have glomerulonephritis? Again, we cannot rule it out, but there is no history of acute disease preceding the chronic stage. It may have been subacute, but if the lesion is sudden and progressive, as this one was, I should expect anemia, which this woman did not have. The likeliest cause for the renal failure seems to have been a pyelonephritis. She was known to have had a colon-bacillus infection. She had costovertebral angle tenderness. The clinical course was consistent with this concept, and the urinary findings were also in keeping. I therefore believe that pyelonephritis was the cause of renal failure, although I cannot rule out syphilitic nephritis.

A few things remain to be answered. Did this patient have cerebrospinal syphilis? We have only a few points to go by, and a spinal-fluid examination was not performed. Eleven years before admission the left pupil was larger than the right. In the absence of any other neurologic signs I should not pay too much attention to it, although transient neurologic signs about the eyes are not infrequent in early central-nervous-system syphilis. If this had been due to syphilis I should have expected more rapid progression of the central-nervous-system disease. Later we hear about ptosis, and if this was

definite, it should be explained. In this case it may easily be explained on the basis of central-nervous-system syphilis, which I think the woman had. The question of cancer was apparently raised by the physician who had the sediment from the ascitic fluid examined in the laboratory. The fluid was described as turbid. If she had an extremely turbid fluid I should be inclined to think that she had destruction of the lymphatic vessels due to malignancy; slightly turbid fluid is not significant. We do not know anything about the specific gravity. I do not see any reason to introduce a new factor in this already complicated picture.

DR. JACOB LERMAN: Would you like to explain the low serum sodium? I am confused by the values.

DR. KLEMPERER: I was somewhat confused myself, because the sodium should fairly well balance the chloride and carbon dioxide. It does not, but I cannot explain this.

DR. LERMAN: Why did they give transfusions?

DR. KLEMPERER: I do not understand that either. On the basis of the data given in the record, one would think that this woman had failure of the left ventricle. If plasma transfusions are given, the patient's blood volume is increased, not only by the amount of fluid given but also by the amount of water drawn into the circulation by the increased osmotic pressure produced by the plasma. The total increase in blood volume may easily overtax an already failing left ventricle. As a matter of fact, this woman died suddenly during a transfusion and, I believe, in pulmonary edema, which may have been related to the transfusions.

### CLINICAL DIAGNOSES

Syphilitic nephritis.
Syphilitic aortic regurgitation.

### DR. KLEMPERER'S DIAGNOSES

Syphilitic aortic regurgitation.
Hypertensive and arteriosclerotic heart disease.
Pyelonephritis?
Syphilitic nephritis?
Syphilis of the central nervous system.

### ANATOMICAL DIAGNOSES

**Nephrosis, probably due to bismuth intoxication.**
**Syphilitic aortitis.**
Septicemia (Type 17 pneumococcus).
Pericarditis, fibrinous.
Pulmonary edema and congestion.
Portal cirrhosis.
Ascites.
Esophageal varices.

### PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The autopsy on this patient showed about 2500 cc. of ascitic fluid, which was probably due to an advanced portal cirrhosis. The liver weighed only 900 gm. and was extremely nodular. She had probably had the condition for years. The spleen was somewhat enlarged, and in the esophagus we found numerous varices, although there was no evidence of hemorrhage from them. The heart was small, weighing only 220 gm., with perhaps slight hypertrophy of the left side. All the valves looked reasonably good. We found no evidence of separation of the aortic cusps at their commissures and no evidence of insufficiency. There were, however, a number of the congenital perforations of the cusps that we see so often. I feel sure that they had nothing to do with the murmurs that were heard. Syphilitic aortitis was present throughout the aorta but not around the mouths of the coronary arteries or in the region of the cusps themselves, and consequently there was no scarring.

DR. PAUL D. WHITE: Do you not believe that there was enough aortitis to dilate the aorta above the valve and in that way to be responsible for the murmur during life?

DR. CASTLEMAN: Possibly; that is the only explanation for the murmur.

DR. WHITE: Evidently there was no marked aortic dilatation post mortem.

DR. CASTLEMAN: No. The lungs showed acute congestion and edema. The kidneys were not remarkable grossly. They weighed about 120 gm. each, somewhat smaller than normal, and they showed slight scarring due to vascular disease. Microscopically, however, we found evidence of severe tubular disease. The convoluted tubules showed marked degeneration, granularity and necrosis of the epithelial cells (Fig. 1). Another finding in the tubules was the presence within some of the nuclei of globular refractile bodies. These bodies were described years ago by Pappenheimer,[2] who believed that they were the result of bismuth intoxication. He later produced the disease experimentally in rats by injecting a bismuth solution. I am certain that these are the same refractile bodies that Pappenheimer found in his cases. We looked carefully for the type of syphilitic kidney disease that was described by Rich but were unable to find any evidence of it. On the other hand, I suppose that one cannot rule out the other type of syphilitic disease of the kidney, the so-called "syphilitic nephrosis," but I am inclined to believe that the lesions are better explained on the basis of bismuth intoxication, that is, a toxic nephrosis of the tubular epithelium due to the bismuth injections. There was no evidence of pyelonephritis or glomerulonephritis. There were a few vascular scars, but no significant nephrosclerosis. She did have a septicemia, which was due to a Type 17 pneumococcus. There was also a fibrinous pericarditis. Could the murmurs in some way have been accounted for by the pericarditis?

DR. WHITE: Who heard the murmurs, and were they confirmed by the visiting staff?

DR. CASTLEMAN: They were heard by many examiners.

DR. WHITE: The murmurs were heard at entry. How long was the patient in the hospital?

DR. CASTLEMAN: Almost three weeks.

DR. WHITE: It is certainly possible to have a to-and-fro pericardial friction rub that resembles murmurs, but it rarely lasts over so long a period of time.

DR. CASTLEMAN: A note was made on the sixteenth day that the heart murmurs were much louder than they had been, with a question of pericardial rub.

DR. WHITE: Do you think she had the pericardial involvement throughout her hospital stay?

DR. CASTLEMAN: No.

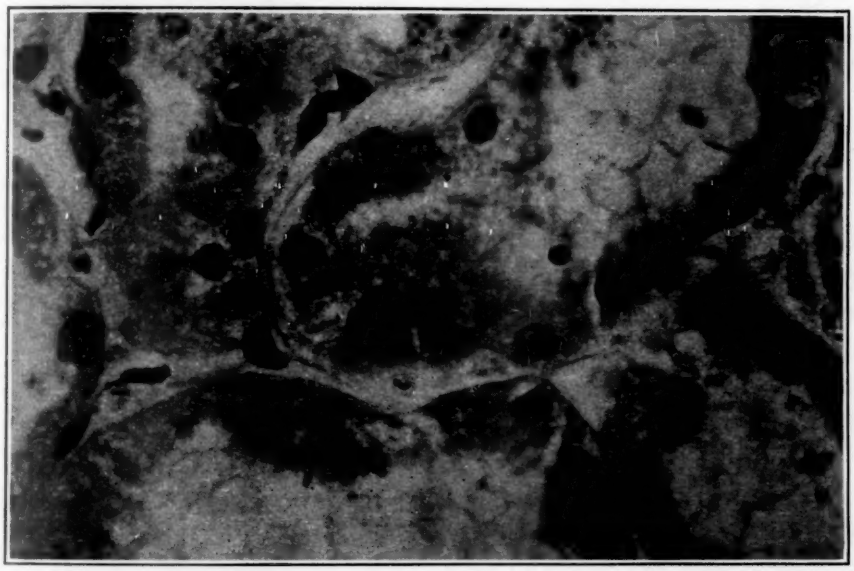

FIGURE 1. *Photomicrograph of Kidney Showing Tubular Degeneration and Intranuclear Bodies.*

DR. WHITE: There remains then some question concerning the exact cause of the murmurs.

DR. T. DUCKETT JONES: I should like to ask Dr. White about the Austin Flint murmur.

This patient never had any evidence of free aortic disease, and one does not hear an Austin Flint murmur unless there is an extremely large heart, practically always with free aortic disease and definite evidence of regurgitation. I wonder if Dr. White would be willing to describe the Austin Flint murmur. I have read the original description[3] over and over, and I have tried to apply it in a number of cases. Often it is in a case in which there is a presystolic murmur, which is, so far as I know, characteristic of mitral stenosis, but I cannot conceive of an aortic process that causes a presystolic crescendo because of the mechanism that it requires. Mitral disease can also produce rumbles in diastole. I wonder if that is Dr. White's idea, or whether he believes that a presystolic murmur can be explained on the basis of an Austin Flint murmur.

DR. WHITE: Dr. E. P. Bagg, of Holyoke, raises the question whether temporary dilatation of the heart could have been responsible for the murmurs at first. Evidently the staff did not find much dilatation of the heart clinically. We cannot settle that question. The x-ray film did not show much of any enlargement.

I agree that the Austin Flint murmurs that I have heard have, as a rule, been in patients who have had marked enlargement of the heart with free aortic regurgitation, due either to syphilis or to rheumatic involvement. In cases with rheumatic involvement one wonders, of course, if there is not some actual mitral stenosis in addition. My conception of the murmur is that it is due, not as originally explained to the pressure of the regurgitant stream of blood going through the aortic valve and compressing the anterior cusp of the mitral valve, thereby producing a functional stenosis, but rather, as Dr. Klemperer has said, to the relative stenosis of the normal mitral ring in comparison with the size of the dilated ventricular cavity. This state of affairs can exist in the cases just cited and in other patients with left ventricular dilatation without aortic regurgitation; in either case there would be the same murmur. Years ago, Dr. Jones, Dr. Bland and I[4] described, in certain cases of acute or subacute rheumatic myocarditis, mitral diastolic murmurs due to such relative mitral stenosis without aortic regurgitation, but in those cases the heart was big and the murmur disappeared when the heart became smaller.

The best Austin Flint murmurs that I have heard

were in Atlanta when I was attending a clinic of cases of well marked, free aortic regurgitation in syphilitic aortitis. Here in New England relatively few Austin Flint murmurs are heard.

I think that I have noted only infrequently a presystolic accentuation at the end of the middiastolic murmur of the Austin Flint type. The auricle in contracting can increase the speed of the blood flow through the mitral ring just before ventricular systole and so theoretically, as well as apparently actually, can increase the murmur started by the simple flow of blood through the valve from auricle to ventricle earlier in diastole, but this presystolic accentuation is not so frequent as accentuation of the middiastolic part of the murmur. Of course, in most cases with mitral stenosis per se and in all such cases with auricular fibrillation, the murmur is mid-diastolic only. In cases with marked presystolic accentuation, the murmur is generally not an Austin Flint murmur.

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## UNITED WAR FUND

When a patient passes the crisis of a serious illness, the physician does not cross the case off his list but maintains a watchful vigilance to aid convalescence and to guard against relapse. In the same way, a nation cannot completely abandon, at the close of a war, certain services, both home and abroad, since these activities must continue through the long period of reconversion.

The Victory Campaign of the Greater Boston United War Fund, which will be conducted October 1 to 17, has a goal of $7,750,000 to help maintain such services. By supporting the coming campaign, physicians in Greater Boston can show that they are not deserting the agencies that administer to the wounds opened by war: they can show they are not ignoring the appeals of the USO, the United Seaman's Service and the groups that give relief to peoples in war-devastated lands. Most important of all, support of the Fund means that they appreciate the value of its Red Feather community services, which must be ready to serve any of the quarter million returning servicemen and servicewomen who need them. It means that they will not fail the social and health centers and the youth and old-age services, which are so necessary to combat the aftershock of war and to keep the Nation healthy.

By endorsing the Fund, the physicians of Greater Boston will once more give whole-hearted support to their communities and to the world beyond.

## RELEASE OF MEDICAL OFFICERS

For a considerable number of combat troops who have seen long service in Europe or in the Pacific some provisions have already been made for orderly release to a civilian status. No official information is available, however, to indicate how soon the majority of medical officers and nurses may expect demobilization. The provisions for the release of men over forty do not apply to officers, particularly those in the Medical Corps. Surgeon General Kirk, in a press and radio conference late last May, let out more than a hint concerning the immediate outlook in this respect. In the course of a review of the excellent state of the health of the Army in this war as compared with that in previous ones, he made the following pertinent statements:

> The Medical Department today is well prepared for the intensification of its work brought about by the cessation of hostilities in Europe. Thousands of wounded veterans in the European and Mediterranean theaters are being transported to the United States as fast as ships and planes are available. . . .
>
> The peak of the Medical Department's activities will not be reached until the fall of 1945. At present, wounded and sick are being returned to this country from all theaters at the rate of 44,000 a month. This evacuation will continue until all of the patients in the European and Mediterranean theaters are removed, which will require ninety days.
>
> The arrival of these thousands of wounded and sick in this country during the next three months will place a heavy load on our general and convalescent hospitals.

The population of all Army hospitals in the United States at present is 290,000. By September, this is expected to reach 315,000, taking into consideration the discharge rate.

It can readily be seen that the Medical Department will be operating at capacity for many months to come, and there will be a critical need for its professional and civilian personnel during this period.

From these remarks it may be inferred that few medical officers and nurses can anticipate early release from service as a result of the victorious conclusion of the war. Doubtless some men who have been taken from key positions in hospitals and medical schools will be relinquished within a reasonable time if sufficient and pressing need for their services is shown, and the office of the surgeon-general has recently indicated that medical officers returned by a theater or declared surplus by a major force, provided their Adjusted Service Ratings are sufficiently high or provided they are over 50 years of age, are eligible for discharge. The majority will have to wait for an undetermined period.

Perhaps the most discouraging news for the medical personnel, although it is proportionately more heartening to the rest of the men in the service, is contained in General Kirk's closing remarks:

Illness and recuperation of wounded and injured men does not cease with a formal declaration of the end of hostilities on any front. The care of those men and women is a continuing responsibility of the Medical Department, which will go on for many months in the future. It will increase rather than diminish . . . .

## MASSACHUSETTS MEDICAL SOCIETY

### COMMITTEE ON LEGISLATION

Reprints of articles appearing in the June 2 issue of the *Journal of the American Medical Association*, relative to the Wagner–Murray–Dingell Bill, have recently been sent to each member of the Society.

Constructive comments as to how the Committee on Legislation can best handle this situation will be greatly appreciated by the committee.

HUMPHREY L. MCCARTHY, *Chairman*

### DEATHS

BRODRICK — Francis S. Brodrick, M.D., of Boston, died September 11. He was in his seventy-eighth year.

Dr. Brodrick received his degree from Wayne University College of Medicine, Detroit, in 1895. He was assistant superintendent of the Boston City Hospital for twenty-five years, having retired in 1937.

GRISWOLD — Merton L. Griswold, M.D., of Uxbridge, died June 10. He was in his seventy-seventh year.

DR. Griswold received his degree from the University of Vermont College of Medicine in 1896.

His widow and two sons survive.

HARKINS — William J. Harkins, M.D., of Quincy, died August 25. He was in his sixtieth year.

Dr. Harkins received his degree from the University of Vermont College of Medicine in 1911. He was associate laryngologist at the Massachusetts General Hospital and assistant surgeon at the Massachusetts Eye and Ear Infirmary. He was consulting surgeon at the Quincy City, Weymouth, Norfolk County, Milton and Hingham hospitals. He was formerly an assistant professor at Harvard Medical School.

His widow and a son survive.

PALMER — Sarah E. Palmer, M.D., of Boston, died August 23.

Dr. Palmer received her degree from the Woman's Medical College of Pennsylvania in 1880 and was the first woman to be admitted to the graduate course in bacteriology at Harvard Medical School. One of the first surgeons to perform cesarean operations, she inaugurated the surgical service at the New England Hospital for Women and Children in 1900. She was a fellow of the American College of Surgeons.

WORTHEN — Clarence F. Worthen, M.D., of Boston, died August 22. He was in his sixty-sixth year.

Dr. Worthen received his degree from Harvard Medical School in 1908. He was ophthalmic surgeon at the Massachusetts Eye and Ear Infirmary, Boston, oculist at the House of Mercy Hospital, Pittsfield, and ophthalmologist at the Newton Hospital. He was a member of the New England Ophthalmological Society and the Newton Medical Society.

His widow and two brothers survive.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### CARE OF CASES OF POLIOMYELITIS IN GENERAL HOSPITALS

It is generally agreed that cases of poliomyelitis can be cared for by general hospitals because the danger to other patients of spread from an active case is relatively small, certainly much less than that of a case of bacillary dysentery. Since this is so, general hospitals can make a contribution to the care of such patients by agreeing to accept them for hospitalization.

In order to care for such patients, a hospital should have on its staff a physician well trained in internal medicine or pediatrics, who can direct the diagnosis and treatment of the disease. The hospital should also have a respirator and at least one person trained in the Kenny technic.

Since it is important that physicians be informed regarding the facilities for the care of poliomyelitis cases, and since the season for an increase in the disease is at hand, the department recently requested information concerning the facilities available throughout the Commonwealth. On the basis of the replies received, the following list of general hospitals that will accept cases of poliomyelitis cases is appended.

| CITY OR TOWN | HOSPITAL | RESPIRATORS |
|---|---|---|
| Beverly | Beverly Hospital | 2 |
| Boston | Boston City Hospital | 8 |
| | Children's Hospital | Several |
| | Forest Hills General Hospital | 0 |
| | Haynes Memorial Hospital | 3 |
| | Massachusetts General Hospital | 4 |
| | New England Hospital for Women and Children (will only accept emergency cases) | 0 |
| | Peter Bent Brigham Hospital (will accept patients over 12 years of age and those younger only in an emergency) | 3 |
| Brookline | Brooks Hospital | 0 |
| Cambridge | Cambridge City Hospital (will only accept emergency cases) | 1 |
| Fall River | Fall River General Hospital | 1 |
| | Union Hospital | 1 |
| Fitchburg | Burbank Hospital (will only accept local cases) | 1 |
| Greenfield | Greenfield Isolation Hospital | 1 |
| Haverhill | Haverhill Municipal Hospital (Hale) (will accept a limited number of local cases) | 1 |
| Holyoke | Holyoke Hospital | 1 |
| Lawrence | Lawrence General Hospital | 2 |
| Leominster | Leominster Hospital | 2 |
| Lowell | Shaw Hospital | 0 |
| | St. John's Hospital | 2 |
| Malden | Malden Hospital (local cases preferred) | 1 |
| Nantucket | Nantucket Cottage Hospital | 0 |
| New Bedford | St. Luke's Hospital | 1 |
| Newburyport | Anna Jaques Hospital | 0* |
| Newton | Newton–Wellesley Hospital | 1 |
| Pittsfield | House of Mercy Hospital | 1 |
| Pocasset | Barnstable County Sanatorium | 0 |
| Quincy | Quincy City Hospital | 2† |
| Salem | Children's Hospital | 2 |
| Springfield | Health Department Hospital | 1 |
| | Mercy Hospital | 0 |
| | Springfield Hospital | 0 |
| Worcester | Belmont Hospital | 1 |
| | Memorial Hospital | 1 |
| | Worcester City Hospital | 3 |

*Newburyport Board of Health has applied for a respirator.
†One adult and one infant respirator.

## CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

| CLINIC | DATE | CLINIC CONSULTANT |
|---|---|---|
| Salem | October 1 | Paul W. Hugenberger |
| Haverhill | October 3 | William T. Green |
| Lowell | October 5 | Albert H. Brewster |
| Brockton | October 11 | George W. Van Gorder |
| Pittsfield | October 15 | Frank A. Slowick |
| Springfield | October 16 | Garry deN. Hough, Jr. |
| Worcester | October 19 | John W. O'Meara |
| Fall River | October 22 | Eugene A. McCarthy |
| Hyannis | October 23 | Paul L. Norton |

## NOTES

Caroline A. Chandler, M.D., has been appointed supervisor of Clinics for Crippled Children, Services for Crippled Children, Massachusetts Department of Public Health. Prior to accepting a commission in United States Public Health Service, Dr. Chandler was with the Division of Research in Child Development, Children's Bureau. She is certified by the American Board of Pediatrics and is a member of the Academy of Pediatrics.

Roy F. Feemster, M.D., has been appointed director of the Division of Local Health Administration, Massachusetts Department of Public Health. He will retain this office for the duration of the military emergency, after which he will return to his former position of director of the Division of Communicable Disease.

Merrill E. Champion, M.D., former epidemiologist in the Massachusetts Department of Public Health, is now acting director of the Division of Communicable Disease.

A. Laurence Corbman, D.D.S., formerly associate dental surgeon with the Office of Indian Affairs, United States Department of the Interior, in South Dakota, has been appointed public-health dental supervisor with the Massachusetts Department of Public Health. He is assisting in a dental-caries study recently authorized by the Legislature in which the use of fluorine for reducing caries among school children is being investigated.

## MISCELLANY

### TUBERCLE BACILLI IN GASTRIC CONTENTS

Any evidence that helps to answer the question of whether or not a patient under treatment for tuberculosis is a source of danger to others is of vital value to the physician, the patient and the public. The examination of gastric contents for the presence of tubercle bacilli is rapidly becoming an essential procedure in those cases in which other tests fail to give a clear-cut answer. (Feld, D. D. Significance of tubercle bacilli in gastric contents. *Am. Rev. Tuberc.* **50**: 481-489, 1944.)

Examination of gastric contents for tubercle bacilli in the fasting patient, although a routine procedure among children at Muirdale Sanatorium since its inception, has only gradually been extended to adults. The now demonstrated importance of the procedure in aiding diagnosis, in guiding therapy, and in evaluating the patient before discharge has come to be recognized rather slowly.

Examination of gastric contents for tubercle bacilli is used by the author on all patients who deny raising sputum or whose sputum is negative. It is also used in cases in which there is doubt concerning the source of the sample presented. Since a single negative gastric aspiration is not considered conclusive, repeated aspirations are performed at intervals. Some patients have cultures of both sputum and gastric contents. Such a procedure expedites the diagnosis of cases with suspected active lesions.

The material used for examination consists of undiluted gastric contents aspirated from fasting patients the first thing in the morning. Previous to 1941, culture and guinea-pig inoculation were done simultaneously on all specimens. Since then only cultures have been used, because they are very accurate and the difference in the results of the two procedures did not warrant continued use of the guinea pig. All specimens are cultured on three slants of Petragnani's medium, and contamination is reported when all three tubes are involved, an infrequent occurrence.

One cannot rely on smears of concentrated specimens of gastric contents for the detection of tubercle bacilli — the number of positives is always small. In certain diagnostic cases animal inoculations, in addition to cultures, are necessary.

The patient who has negative sputum cultures, but who has tubercle bacilli only by gastric examination, is not a so-called "innocuous patient." In our survey we observed 21 such patients who on subsequent sputum examination were positive on concentrated smear or culture. Therefore, these patients can and do develop subsequent positive sputum.

A patient with a positive gastric content should be treated exactly like a patient with a positive sputum.

Before the author's patients are discharged it is necessary that they have negative gastric aspirations in the absence of sputum. This is done to avoid the discharge of active cases. In order for a patient to be discharged with medical advice as inactive he must have at least five successive negative examinations. If negative on those examinations, and if other findings warrant it, the patient is discharged as having no evidence of active disease.

During the past five years, 868 adults at Muirdale Sanatorium had a total of 4204 examinations of gastric contents. Of these, 404 (46.4 per cent) had negative gastric contents; they received 1338 examinations. The remaining 464 (53.6 per cent) cases had 2866 examinations, of which 1271 (44.3 per cent) were positive. The number of examinations per case varied, the average for the negative group being 3.3 per case, and for the positive group 6.2. The number of repeats depends on the individual case, just as in sputum examinations.

Thus there are two groups of patients — those with positive and those with negative gastric contents. Each of these groups in turn is divided into three subgroups: the no-sputum group, the negative-sputum group and the positive-sputum group.

No fine line of distinction can be drawn between these three subgroups. Occasionally patients deny raising sputum and yet the specimens they send in contain tubercle bacilli. Also, there are patients who state they raise sputum, when the sample is only saliva or secretions from a chronic nasopharyngitis common in the locality. It is realized that, if numerous and timely sputum examinations were done, a small percentage would have proved positive. This is not deemed economically advisable, as valuable time may be lost. Instead, a simple reliable gastric aspiration can be done with culture results known in a few weeks.

Significantly, 21 (7.5 per cent) of 282 patients became sputum-positive after being positive at first only on gastric aspiration. This occurred on the average of about six months later. This small group of patients reveals an important fact because, as has been previously pointed out, these cases cannot be considered as harmless, and careful observation and timely sputum examinations will prove that some of these cases are sputum-positive.

It is important to do consecutive gastric examinations on adult patients in whom it is impossible to determine the status of activity from a roentgenogram and in whom the sputum, if present, is negative. If 5 consecutive aspirations are negative on culture, it is likely that there is no evidence of active pulmonary tuberculosis.

Of the 404 patients in our series who never had a positive gastric aspiration, there were 224 who had either no sputum or negative sputum. In spite of the diagnosis of pulmonary tuberculosis on admission the author feels justified in recording a case as having no evidence of active tuberculosis if a series of gastric aspirations is negative, as well as sputum cultures.

The remaining 180 of the 404 with negative gastric contents had, at some time, tubercle bacilli in the sputum. The main reason that there were no positive aspirations in this group is because, in most of these patients, the examinations followed by some ten months a positive sputum, and many of these patients were on the road to recovery.

It is possible, however, to have a negative gastric content and a positive sputum, which does not invalidate the reliability of this procedure. There were several patients who became gastric-content-negative and sputum-negative and then later became sputum-positive. Unstable cases of tuberculosis are likely to fluctuate like this.

In the past year and a half it has been the author's policy to do 5 consecutive aspirations or negative cases. If these examinations are negative by culture, the patient is considered as having no evidence of active pulmonary tuberculosis. In the majority of cases it is wise to hold these patients for observation until the cultures are completed. Of the cultures, over 95 per cent, where positive, will show growth within six weeks; however, the cultures are kept until eight weeks. The patient is then re-examined by x-ray and his case is re-evaluated. Most of these are discharged with no clinical evidence of active tuberculosis. — Reprinted from *Tuberculosis Abstracts*, September, 1945.

## NOTE

On August 24, the Salem Tumor Clinic sponsored a teaching clinic at the Salem Hospital. Dr. Ira T. Nathanson, of Boston, gave a talk entitled "Head and Neck Cancer"; this was attended by staff members of the Salem Hospital, several visiting physicians from surrounding communities and a number of nurses.

# CORRESPONDENCE

## DR. RUSHMORE RETIRED AS DEAN

*To the Editor*: I should like to inform the medical profession, through the courtesy of the *Journal*, that I am no longer dean of the School of Medicine, Middlesex University, having been retired recently by vote of the Trustees of the University, which vote was worded to take effect immediately. I am devoting myself to the practice of obstetrics and gynecology.

STEPHEN RUSHMORE, M.D.

## MEDICAL AND PUBLIC-HEALTH PERSONNEL NEEDED IN CHINA

*To the Editor*: The Chinese Government has requested UNRRA to provide, as soon as possible, some two hundred field personnel of the following categories to strengthen the available Chinese personnel. Such personnel will be required to head the respective services in hospitals of 100 to 250 beds, which will be established in areas recently liberated from the Japanese.

General surgeons
Orthopedic surgeons
Genitourinary surgeons
Gynecologists and obstetricians
General physicians
Dermatologists and syphilologists
Ophthalmologists
Otolaryngologists
Radiologists
Dentists
Pediatricians
Laboratory technicians
X-ray technicians
Sanitary engineers
Public-health engineers
Public-health nurses
Clinical nurses

General practitioners with some specialist experience will be acceptable. Candidates should be under fifty-five years of age and in good physical condition.

Will those interested please write to me at UNRRA, 1344 Connecticut Avenue, N.W., Washington 25, D. C.

Szeming Sze, M.D., *Chief*
Far East Section, Health Division

United Nations Relief and
Rehabilitation Administration
1344 Connecticut Avenue, N.W.
Washington 25, D.C.

# NOTICES

## ANNOUNCEMENTS

Dr. Charles P. Sheldon announces the opening of an office at 270 Commonwealth Avenue, Boston.

Dr. Theodore L. Badger, who has recently returned from overseas duty with the Army of the United States, announces the reopening of his office at 264 Beacon Street, Boston, for the practice of medicine, particularly as it concerns diseases of the lungs.

Dr. Paul L. Sandi announces the removal of his office from 204 Hanover Street to 636 Beacon Street, Boston.

(*Notices continued on page xxi*)

NOTICES (*Continued from page 398*)

## NEW ENGLAND OTO-LARYNGOLOGICAL SOCIETY

The regular fall meeting of the New England Oto-Laryngological Society will be held at the Massachusetts Eye and Ear Infirmary on Wednesday, October 3.

PROGRAM

Regular Wednesday conference at 11 a.m.
Instructional courses from 2 to 3 p.m.
Business meeting.
Speakers from 4 to 6 p.m.
No evening session.

## SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, OCTOBER 4

FRIDAY, OCTOBER 5
*9:00–10:00 a.m. Medical clinic. Isolation Amphitheater, Children's Hospital.
10:50 a.m. Postgraduate clinic in dermatology and syphilology. Amphitheater, Dowling Building. Boston City Hospital.

SATURDAY, OCTOBER 6
*10:00 a.m.– 12:00 m. Medical staff rounds. Peter Bent Brigham Hospital.

MONDAY, OCTOBER 8
*12:00 m.–1:00 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

TUESDAY, OCTOBER 9
*9:00–10:00 a.m. Medical clinic. Infants' Hospital.
*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

WEDNESDAY, OCTOBER 10
*12:00 m. Clinicopathological conference. Children's Hospital.
*12:00 m.–1:00 p.m. Clinicopathological conference. Cambridge Hospital.

*Open to the medical profession.

OCTOBER 1–6. Medicolegal conference and seminar. Page 776, issue of June 28.

OCTOBER 1–DECEMBER 10, 1945 and JANUARY 7–APRIL 22, 1946. Metropolitan State Hospital. Eleventh postgraduate seminar in neurology and psychiatry. Page 314, issue of September 6.

OCTOBER 3. New England Oto-Laryngological Society. Notice above.

OCTOBER 8–19. Eighteenth Graduate Fortnight, New York Academy of Medicine. Page xvii, issue of September 20.

OCTOBER 11. Calcareous Deposits in the Urinary Tract: Etiology, diagnosis and treatment. Dr. George Gilbert Smith. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

## DISTRICT MEDICAL SOCIETY

WORCESTER

OCTOBER 10. Rutland State Hospital.
NOVEMBER 14. Grafton State Hospital.
DECEMBER 12. Worcester City Hospital.
JANUARY 9. St. Vincent Hospital.
FEBRUARY 13. Worcester State Hospital.
MARCH 13. Worcester Memorial Hospital.
APRIL 10. Hahnemann Hospital.
MAY 8. Annual meeting.


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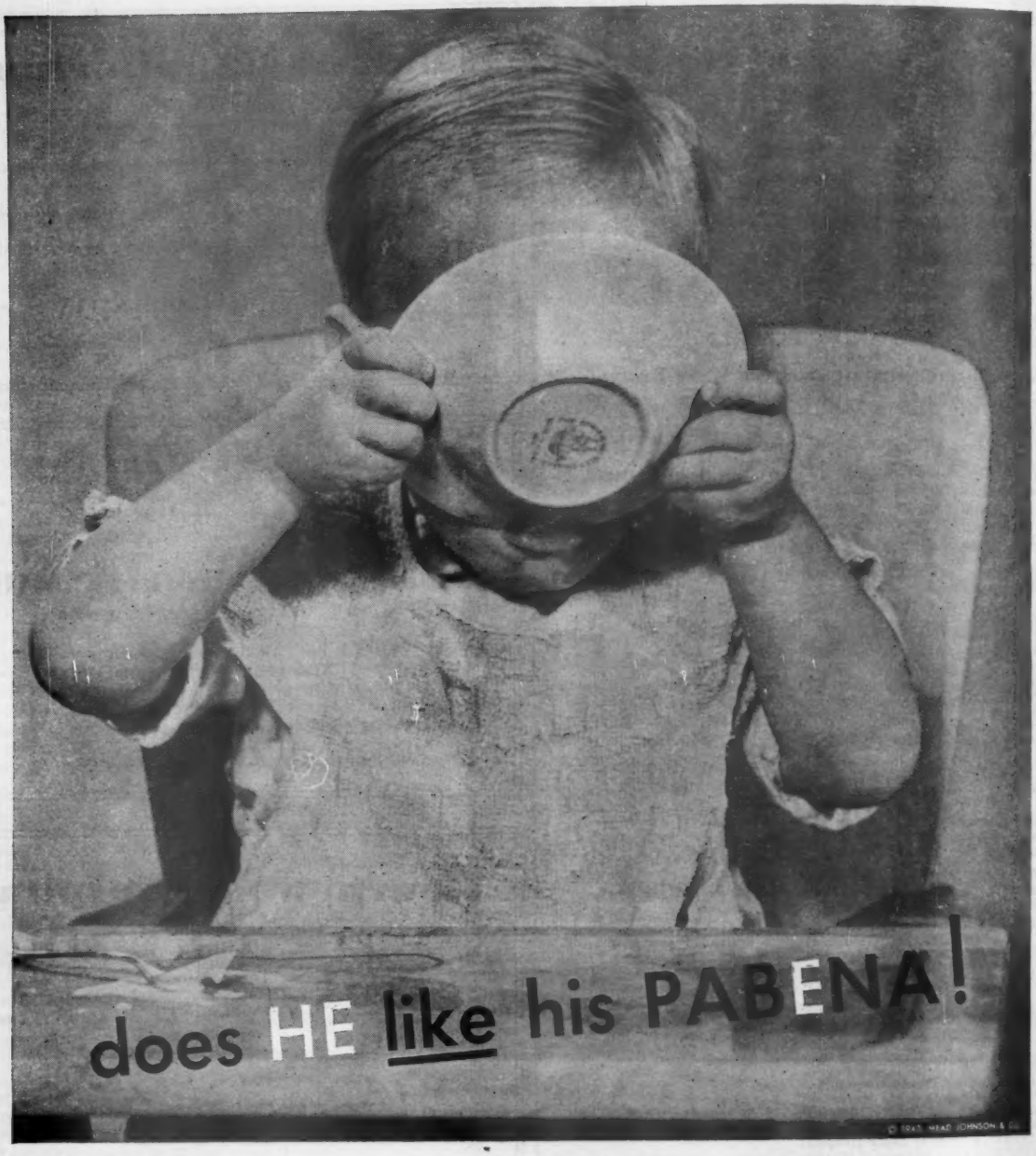


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